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INTAKE OF POTASSIUM, AN IMPORTANT CONSIDERATION IN ADDISON'S DISEASE

A METABOLIC STUDY

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It has long been recognized that injections of sodium chloride are of benefit in the treatment of the characteristic crises of Addison's disease, but it was the quantitative investigation of the electrolytes of the plasma by Loeb and his associates [1] and by Harrop and his associates [2] that first revealed why large amounts of sodium and chloride are required effectively to combat such crises. Their experiments demonstrated that the loss of ions of sodium and chloride is one of the principal disturbances leading to the development of the crisis and that the crisis can be prevented by a quantitative replacement of these ions. However, the results obtained by treating patients only with sodium chloride have remained less satisfactory than those obtained when extract of adrenal cortex has been given, and no one has succeeded in maintaining indefinitely the life of a completely adrenalectomized dog by administering only sodium chloride. Thus, for some time it has been evident that the

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1. Loeb, R. F.; Atchley, D. W.; Benedict, Ethel M., and Leland, Jessica: Electrolyte Balance Studies in Adrenalectomized Dogs with Particular Reference to Excretion of Sodium, J. Exper. Med. **57**:775-792 (May) 1933.

2. Harrop, G. A.; Soffer, L. J.; Ellsworth, Read, and Trescher, J. H.: Studies on Suprarenal Cortex: III. Plasma Electrolytes and Electrolyte Excretion During Suprarenal Insufficiency in the Dog, J. Exper. Med. **58**:17-38 (July) 1933.

course of Addison's disease is influenced unfavorably by factors other than the supply of sodium chloride.

The next step was the identification of one of these other factors by Harrop and his associates [3] and simultaneously by Allers and one of us (Dr. Kendall),[4] working independently. This, namely, is the requirement of more ions of sodium than of chloride. Harrop observed that the excretion of sodium was greater than the excretion of chloride if sodium chloride alone was given to adrenalectomized dogs and that while neither sodium chloride nor sodium bicarbonate would maintain the lives of such animals, the simultaneous administration of these salts would do so. Allers and Kendall, attempting to maintain adrenalectomized dogs with sodium chloride alone, made the observation that the alkali reserve of the blood fell to low levels, and they suspected that acidosis was responsible for the failure of these animals to survive. The urea content of the blood, which usually is markedly elevated in conditions of severe adrenal insufficiency, was not elevated in animals receiving large amounts of sodium chloride; and when the acidosis was corrected by supplying extra base, as sodium in the form either of sodium bicarbonate or of sodium citrate, the dogs remained in excellent condition for indefinite periods.

The probable bearing of these observations on the successful treatment of Addison's disease was emphasized for us by the discovery of a patient who, in addition to having a spontaneous craving for salt, such as frequently occurs in Addison's disease, which she satisfied by eating salt, took generous quantities of sodium bicarbonate because of pyrosis. She had preserved her weight and strength without other treatment for five years. The results obtained, however, by treating other patients with sodium bicarbonate or sodium citrate and sodium chloride remained less satisfactory than was desirable. Patients would do well for weeks or months and then, for no apparent reason, would fail and would require injections of extracts of adrenal cortex. Thus, other uncontrolled factors still remained unrecognized.

Although the results obtained by Harrop and his co-workers and by Kendall and Allers [5] were similar in regard to the necessity for administering extra sodium ion with sodium chloride, they were not similar

3. Harrop, G. A.; Soffer, L. J.; Nicholson, W. M., and Strauss, Margaret: Studies on Suprarenal Cortex: IV. The Effect of Sodium Salts in Sustaining the Suprarenalectomized Dog, J. Exper. Med. **61**:839-860 (June) 1935.

4. Allers, W. D.: Influence of Diet and Mineral Metabolism on Dogs After Suprarenalectomy, Proc. Staff Meet., Mayo Clin. **10**:406-409 (June 26) 1935. Allers, W. D.; Nilson, N. W., and Kendall, E. C.: Studies on Adrenalectomized Dogs: The Toxic Action of Potassium, ibid. **11**:283-288 (April 29) 1936.

5. Kendall, E. C.; Mason, H. L.; Myers, C. S., and Allers, W. D.: A Physiologic and Chemical Investigation of the Suprarenal Cortex, J. Biol. Chem. **114**:lvii-lviii, 1936.

in regard to the maintenance of the normal level of electrolytes in the blood. The former authors stated that "it is only by the exhibition of both extract and salt in adequate amounts that entirely normal plasma electrolyte levels may be sustained in the totally suprarenalectomized dog." They did not attempt to give a diet which was either low or uniform in its content of potassium. The adrenalectomized dogs treated by Kendall and Allers with sodium chloride and sodium citrate were given a diet with an unusually low content of potassium. Under these conditions not only could the animals be maintained indefinitely without the use of extracts of adrenal cortex, but the level of the electrolytes in the plasma also remained entirely normal. Furthermore, adrenalectomized dogs maintained only with sodium chloride and sodium bicarbonate or citrate without the use of extract of adrenal cortex were found to be surprisingly sensitive to small amounts of potassium in the diet. If 0.5 Gm. of potassium was added to the daily diet of such dogs, a state of crisis was produced like that of acute adrenal deficiency. This occurred even when the animals were receiving liberal supplies of the sodium salts named.[6]

A preliminary observation in a case of Addison's disease seemed to indicate that patients similarly are sensitive to the addition of potassium to their diet. The following investigation was therefore undertaken to determine: (1) whether higher intakes of potassium would consistently provoke substantial losses of sodium and chloride and thus favor the development of symptoms of crisis and (2) whether restricting the intake of potassium might be advantageous in the maintenance of patients with Addison's disease, in particular whether such restriction might lessen the requirement for sodium salts and extract of adrenal cortex.

PROCEDURE

Three patients were chosen for investigation; two of them had previously been the subjects of metabolic observations, and symptoms of crisis had developed on withdrawal of sodium chloride from the diet. All revealed the characteristic pigmentation and other typical symptoms of Addison's disease. They were placed in the hospital under close supervision, and special care was exercised to make complete collections of the urine, this being further controlled by daily determinations of the excretion of creatinine.

Constant diets were served, planned so that their content of ions of sodium approximated 0.59 Gm., of chloride 0.91 Gm. and of potassium 1.6 Gm., except that in period 2 in case 3 (table 3) the food was made to contain 5.8 Gm. of potassium. The composition of the diets in sodium, chloride and potassium

6. Confirmation of these observations by experiments performed on cats and rats has appeared in a paper by Zwemer and Truszkowski (Science **83**:558-560 [June 5] 1936) since the preparation of this manuscript.

was estimated from the tables of Sherman.[7] The levels of intake of sodium, chloride and potassium were increased in various periods by the addition to the diet or the administration separately of weighed amounts of the salts of these substances.

ANALYTIC METHODS

Urine.—The various constituents of urine were determined by the following analytic methods:

Nitrogen: Macro-Kjeldahl.

Chloride: Volhard.

Sodium: Gravimetric determination of sodium as sodium zinc uranyl acetate, using the method of Barber and Kolthoff,[8] as modified by Butler and Tuthill.[9]

Preformed creatinine: Folin.[10]

Total creatinine: Folin, the urine being boiled with trinitrophenol.

Potassium: Fiske and Litarczek [11] and Folin.[12]

The Fiske and Litarczek method of analysis for potassium is based on a preliminary precipitation of potassium as potassium cobaltinitrite and final precipitation as potassium bitartrate. The following precautions and slight modifications proved to be of value: Extreme care was necessary in washing the precipitate of tartrate to insure complete removal of the excess of tartaric acid from the precipitate. The alcohol was allowed to pass through the filter pads at a rate of about 1 cc. in three or four minutes. Instead of transferring the filter pads after the final precipitation, the precipitated tartrate was removed by allowing hot water to pass slowly through the filter pads so that the potassium bitartrate was completely dissolved. This permits the use of the same filter pads for a series of determinations. A more dilute solution of sodium hydroxide (0.005 to 0.01 normal) was used for the final titration, and the solution was stirred during titration with air freed from carbon dioxide. An 0.02 per cent solution of phenol red was used as the indicator. Under these conditions, with a solution of purified potassium chloride containing from 2 to 4 mg. of potassium, the average recovery of potassium was 99.6 per cent. The data reported were obtained both from ashed and from unashed samples, with, in general, excellent duplication of

7. Sherman, H. C.: Chemistry of Food and Nutrition, ed. 3, New York, The Macmillan Company, 1926, p. 587.

8. Barber, H. H., and Kolthoff, I. M.: A Specific Reagent for the Rapid Gravimetric Determination of Sodium, J. Am. Chem. Soc. **50**:1625-1631 (June) 1928; Gravimetric Determination of Sodium by the Uranyl Zinc Acetate Method: II. Application in the Presence of Rubidium, Cesium, Potassium, Lithium, Phosphate or Arsenate, ibid. **51**:3233-3237 (Nov.) 1929.

9. Butler, A. M., and Tuthill, Elizabeth: An Application of the Uranyl Zinc Acetate Method for Determination of Sodium in Biological Material, J. Biol. Chem. **93**:171-180 (Sept.) 1931.

10. Folin, Otto: On the Determination of Creatinine and Creatine in Urine, J. Biol. Chem. **17**:469-473, 1914.

11. Fiske, C. H., and Litarczek, George: A New Method for Potassium, J. Biol. Chem. **67**:xvi-xvii, 1926.

12. Folin, Otto: Laboratory Manual of Biological Chemistry, ed. 5, New York, D. Appleton-Century Company, Inc., 1934, pp. 177-179 and 239.

results. If, however, the specimens of urine had been made acid with sulfuric acid to prevent a loss of nitrogen, satisfactory results could be obtained only by ashing the samples before the analysis was made. If hydrochloric acid had been used, ashing was not necessary, although in all cases a preliminary evaporation of the sample was made in order to remove the excess acid.

Blood Serum.—The following analytic methods were used for blood serum:

Sodium: Butler and Tuthill's modification of Barber and Kolthoff's method.

Chloride: Open Carius method as applied by Van Slyke.[13]

Potassium: A dry sodium cobaltinitrite reagent was prepared according to the method of Fiske and Litarczek. The determinations were made of extracts of serum ashed in the muffle, with the precautions necessary to avoid loss of potassium and sodium. The potassium was precipitated as sodium potassium cobaltinitrite, according to the conditions of Fiske and Litarczek but omitting digestion with nitrohydrochloric acid. The precipitate was centrifugated, and the potassium was titrated with potassium permanganate, according to the method of Kramer and Tisdall.[14]

PROTOCOLS

CASE 1.—*Observation as to the Effect of the Level of Intake of Potassium on Addison's Disease.*—The subject of this study was a woman 39 years of age who, except for minor ailments, was well until August 1933. She then began to lose weight and strength and observed increasing pigmentation of the skin. In August 1934 she became suntanned, and the tan never faded. After April 1935 the pigmentation became deeper, and weakness increased to such an extent that the patient took to her bed. She recently had been treated with injections of a commercial extract of adrenal cortex[15] and for several months had of her own accord been taking extra sodium chloride by mouth because of a marked craving for it. She first came to the clinic and was admitted to the hospital on Nov. 11, 1935.

Examination revealed diffuse pigmentation of the skin and mucous membranes, associated with many black freckles. The systolic blood pressure in millimeters of mercury was 92 and the diastolic 64. Roentgenograms revealed no evidence of tuberculosis of the lungs and no calcification in the region of the adrenal glands. The flocculation test for syphilis was negative. The values for the sodium chloride in and for the carbon dioxide-combining power of the blood were normal. The value for blood urea also was normal.

Observations from November 15 to December 2 (metabolic data in table 1 and chart 1, period 1): On November 15 the daily intake of potassium was lowered to an amount not greater than 1.6 Gm. This was accomplished by suitably adjusting the diet. For the next ten days 12 Gm. of extra sodium chloride was administered daily by mouth, making a total intake of about 18 Gm. of sodium chloride. Five grams of sodium citrate also was given daily. Adrenal cortex

13. Van Slyke, D. D.: The Determination of Chlorides in Blood and Tissues, J. Biol. Chem. **58**:523-529 (Dec.) 1923.

14. Kramer, Benjamin, and Tisdall, F. F.: A Clinical Method for Quantitative Determination of Potassium in Small Amounts of Serum, J. Biol. Chem. **46**:339-349 (April) 1921.

15. The preparation used was eschatin.

extract [16] was withheld. The condition of the patient remained very good; in fact, it was distinctly better than at the time of her admission to the hospital. She was able to get up from bed and to be around in the halls of the hospital every day. She slept well and ate practically all the food that was served to her.

TABLE

	Intake										Twenty-Four Hour Urine									
	Extract of Adrenal Cortex				Total Sodium		Total Chloride		Total Potassium						Sodium		Chloride		Potassium	
Date	Lot	Amount, Cc.	Sodium Chloride, Gm.	Sodium Citrate, Gm.	Gm.	Millimols	Gm.	Millimols	Gm.	Millimols	Total Nitrogen, Gm.	Volume, Cc.	Creatinine Nitrogen, Gm.	Total Nitrogen, Gm.	Creatine Nitrogen, Mg.	Gm.	Millimols	Gm.	Millimols	Gm.
Nov. 1935																				
15	..	..	18.0	5	8.07	350	11.00	308	1.6	41	6.2	.....	....	....	..	....	...	....	...	....
16	..	..	18.0	5	8.07	350	11.00	308	1.6	41	6.7	2,140	0.29	6.60	35	7.40	324	9.61	270	1.40
17	..	..	18.0	5	8.07	350	11.00	308	1.6	41	5.9	1,250	0.26	5.06	42	5.23	228	6.40	180	1.06
18	..	..	18.0	5	8.07	350	11.00	308	1.6	41	5.6	1,310	0.27	4.65	25	5.89	256	7.47	210	1.14
19	..	..	18.0	5	8.07	350	11.00	308	1.6	41	6.6	745	0.21	3.31	11	2.82	123	3.29	91	0.65
20	..	..	18.0	5	8.07	350	11.00	308	1.6	41	6.9	1,460	0.25	3.70	3	4.27	186	4.79	135	0.79
21	..	..	18.0	5	8.07	350	11.00	308	1.6	41	6.7	1,465	0.29	4.28	5	4.29	187	5.00	140	0.97
												Period 1.—Effect of Restricting Intake of Sodium								
22	..	..	18.0	5	8.07	350	11.00	308	1.6	41	6.6	1,145	0.30	4.75	1	5.21	226	6.64	187	1.21
23	..	..	18.0	5	8.07	350	11.00	308	1.6	41	6.7	1,070	0.18	2.82	1	3.89	169	5.11	144	0.66
24	..	..	18.0	5	8.07	350	11.00	308	1.6	41	6.6	1,660	0.29	4.73	7	6.15	268	8.14	228	1.18
25	..	..	6.0	..	2.37	103	3.65	103	1.6	41	6.6	1,380	0.27	4.34	16	5.40	235	6.86	193	0.87
26	..	..	6.0	..	2.37	103	3.65	103	1.6	41	6.9	1,545	0.29	4.60	9	3.48	151	4.53	128	0.86
27	..	..	1.5	..	0.59	26	0.91	26	1.6	41	6.6	1,400	0.27	4.33	12	2.64	115	3.17	89	0.81
28	..	..	1.5	..	0.59	26	0.91	26	1.6	41	6.9	1,100	0.28	4.50	9	2.45	107	2.94	83	0.81
29	..	..	1.5	..	0.59	26	0.91	26	1.6	41	6.7	990	0.27	4.48	19	2.01	88	2.48	70	0.80
30	..	..	1.5	..	0.59	26	0.91	26	1.6	41	5.9	735	0.24	4.62	21	1.55	68	1.89	53	0.87
Dec.																				
1	..	..	1.5	..	0.59	26	0.91	26	1.6	41	6.4	895	0.27	4.72	44	1.17	51	1.54	43	0.90
2	..	..	18.2	2	7.59	330	11.10	313	1.6	41	3.7	875	0.29	4.65	78	0.88	38	1.08	31	0.86
3	..	..	16.0	5	7.27	317	9.75	275	1.6	41	4.6	1,040	0.25	4.69	75	2.10	91	3.44	97	1.34
4	..	..	16.0	5	7.27	317	9.75	275	1.6	41	5.8	1,245	0.28	4.96	68	3.30	144	4.93	138	1.72
5	..	..	16.0	5	7.27	317	9.75	275	1.6	41	4.6	1,320	0.24	3.58	30	3.47	150	4.33	122	1.36
6	..	..	16.0	5	7.27	317	9.75	275	1.6	41	6.7	1,160	0.20	2.77	16	2.79	122	3.20	90	0.95
7	52	10	16.0	5	7.27	317	9.75	275	1.6	41	6.4	1,750	0.29	4.03	9	4.09	178	4.78	135	1.46
8	52	10	16.0	5	7.27	317	9.75	275	1.6	41	6.7	1,073	0.26	4.17	3	3.67	160	4.22	119	1.25
9	..	..	16.0	5	7.27	317	9.75	275	1.6	41	6.6	1,073	0.26	4.17	0	3.67	160	4.22	119	1.25
10	..	..	16.0	5	7.27	317	9.75	275	1.6	41	4.8	1,340	0.26	4.07	7	5.22	227	6.16	176	0.99
11	..	..	16.0	5	7.27	317	9.75	275	1.6	41	4.1	1,387	0.27	3.77	0	5.11	222	6.49	183	0.91
12	..	..	16.0	5	7.27	317	9.75	275	1.6	41	6.7	1,387	0.27	3.77	1	5.11	222	6.49	183	0.91
13	..	..	16.0	5	7.27	317	9.75	275	1.6	41	6.6	1,380	0.30	4.08	15	3.73	162	4.60	132	0.94
14	..	..	16.0	5	7.27	317	9.75	275	1.6	41	6.6	1,400	0.29	3.71	12	4.03	175	5.10	143	0.72
																				Period 2.—Effe
15	..	..	16.0	5	7.27	317	9.75	275	1.6	41	6.6	1,495	0.29	3.23	18	3.37	147	4.45	125	0.98
16	..	..	16.0	5	7.27	317	9.75	275	4.0	102	6.6	1,800	0.29	3.27	21	4.59	191	5.68	160	0.97
17	..	..	16.0	5	7.27	317	9.75	275	4.0	102	6.7	2,060	0.27	3.14	13	6.82	297	8.44	237	1.70
18	..	..	6.0	..	2.37	103	3.65	103	4.0	102	6.6	1,984	0.26	3.16	5	5.54	241	7.04	198	1.83
19	..	..	6.0	..	2.37	103	3.65	103	4.0	102	6.9	1,984	0.26	3.16	5	5.54	241	7.04	198	1.83
20	52	20	26.0	10	12.19	529	15.85	445	4.0	102	6.7	2,055	0.36	3.36	2	6.47	281	8.12	229	2.78
21	..	..	16.0	5	7.27	317	9.75	275	4.0	102	6.6	2,150	0.30	4.86	11	7.84	341	9.26	261	4.18
22	..	..	16.0	5	7.27	317	9.75	275	4.0	102	5.4	1,570	0.26	4.00	35	5.55	242	7.11	200	2.45
23	..	..	6.0	..	2.37	103	3.65	103	4.0	102	5.8	2,030	0.27	3.95	11	5.12	223	6.52	183	2.19
24	..	..	26.0	10	12.19	529	15.85	445	4.0	102	6.9	2,060	0.28	4.21	14	4.41	192	6.00	169	2.46
25	..	..	16.0	5	7.27	317	9.75	275	1.6	41	6.6	1,410	0.29	4.40	13	4.20	183	4.60	130	2.43
26	..	..	11.0	2.5	4.83	210	6.72	189	1.6	41	6.9	1,300	0.31	4.36	29	4.74	206	6.03	170	1.82
27	..	..	11.0	2.5	4.83	210	6.72	189	1.6	41	6.4	1,100	0.31	3.48	17	3.17	138	4.34	122	0.98
28	..	..	11.0	2.5	4.83	210	6.72	189	1.6	41	6.4	1,140	0.27	2.80	14	2.96	129	4.06	116	0.95
29	..	..	11.0	2.5	4.83	210	6.72	189	1.6	41	6.4	1,420	0.29	3.12	..	3.25	141	4.69	134	1.17

16. Except when otherwise specified, the extract of adrenal cortex administered in these cases was cortin prepared in the laboratory of the Division of Biochemistry of the Mayo Foundation.

On November 25 the extra sodium salts were withheld. This reduced the intake of sodium chloride to about 6 Gm. a day, namely, to the salt naturally contained in the food and the 4.5 Gm. of sodium chloride used in seasoning the food. On November 27 the sodium chloride used as seasoning was omitted,

TABLE I. *...a in Case 1*

Blood Plasma									Blood Pressure, Mm. of Mercury		
Potassium	Sodium	Chloride									
Gm.	Millimols per Liter	Mg. per 100 Cc.	Millimols per Liter	Potassium, Mg. per 100 Cc.	Urea, Mg. per 100 Cc.	Sugar, Mg. per 100 Cc.	Carbon Dioxide, Vol. per 100 Cc.	Body Weight, Kg.	Systolic	Diastolic	Clinical Observations
....	128	375	106	....	24	80	61	60.7	78	50	Began diet low in potassium
1.40	133	377	107	....	..	85	57	60.0	84	56	
1.06	...	...	...	....	..	..	..	60.0	82	54	
1.14	137	375	106	....	24	76	58	60.0	68	54	Occasional nausea
0.65	137	374	106	15.7	..	..	..	60.0	90	64	Stronger
0.79	...	...	...	....	..	..	..	59.5	90	62	No change
0.97	139	371	105	18.2	18	75	57	59.3	88	60	
Sodium ...oride, with Intake of Potassium at a Low Level											
1.21	...	...	...	....	..	..	..	60.2	84	70	Stronger
0.66	141	376	106	15.8	18	76	55	60.2	78	56	No change
1.18	...	...	...	....	..	..	..	....	70	54	
0.87	140	371	105	16.3	18	91	52	60.1	80	64	
0.86	...	...	...	....	..	..	..	59.5	68	54	
0.81	141	374	106	16.3	18	77	49	60.0	78	68	
0.81	...	...	...	....	..	..	..	58.6	80	62	Weaker
0.80	137	363	102	17.2	21	..	..	57.9	80	55	Weaker; sleepless
0.87	134	354	100	17.9	24	88	52	57.7	88	76	
0.90	130	343	97	20.4	24	97	57	57.7	72	50	Nausea; slept well
0.86	129	337	95	19.8	27	106	51	....	86	52	Very weak; sleepless
1.34	133	365	103	19.9	36	90	49	58.4	86	58	
1.72	...	...	...	....	..	..	..	58.6	85	56	Stronger
1.36	...	...	...	....	..	..	..	59.0	88	55	
0.91	...	...	...	....	..	..	..	59.1	76	42	Hiccup; still weak
1.46	...	...	...	....	..	..	..	59.1	84	42	Remains weak
1.33	...	...	...	....	..	..	..	59.5	80	52	Much stronger
1.35	137	388	109	....	18	74	50	60.0	72	54	Low abdominal cramps
0.99	...	...	...	....	..	..	..	59.9	78	56	Menstruation began
0.91	...	...	...	....	..	..	..	....	78	42	Stronger
0.93	...	...	...	....	..	..	..	59.3	80	64	Much improved
0.94	...	...	...	....	..	..	..	59.1	80	64	As well as on entry
0.73	...	...	...	....	..	..	..	59.1	80	62	No change
2.—Effe...reasing Intake of Potassium											
0.98	...	...	...	....	..	..	..	59.9	74	48	Doing well
0.97	...	...	...	....	..	..	..	59.7	78	48	No change
1.70	...	...	...	....	..	..	..	59.1	72	62	No change
1.83	146	383	110	18.5	14	80	53	59.5	74	52	No change
1.83	141	381	109	18.3	14	88	50	58.2	68	48	Much weaker
2.78	137	377	106	18.1	15	83	53	58.2	80	48	Very sick
4.18	...	...	...	....	..	..	..	58.6	86	58	Improved
2.45	...	...	...	....	..	..	..	58.9	82	48	Same
2.19	137	376	106	....	21	76	52	58.6	78	60	Much weaker; nauseated
2.46	137	373	104	17.3	15	86	50	57.7	78	64	Improved by evening
2.43	...	...	...	....	..	..	..	59.5	88	58	Much stronger
1.82	...	...	...	....	..	..	..	59.9	84	66	Satisfactory
0.98	...	...	...	....	..	..	..	59.2	78	58	
0.95	...	...	...	....	..	..	..	59.0	82	64	
1.17	...	...	...	....	..	..	..	58.6	84	50	Feels well

which reduced the intake of sodium chloride to not more than 1.5 Gm. On November 27 the patient felt well and that night slept well. On the following day, November 28, she was weaker, and on November 29 she was unable to walk to the scales to be weighed. Her sleep was somewhat disturbed by restlessness;

nevertheless, she continued to feel well, and nausea, hiccup, abdominal pain and other symptoms of impending crisis were absent. In addition, the pulse was strong, and all the food served was eaten. On December 2, the eighth day after the intake of sodium and chloride had been restricted, the patient fainted while being weighed. Restlessness was increasing, and there was some nausea. Despite this the patient's condition did not suggest the development of a definite crisis.

During this period of seven days in which the patient had been deprived of sodium chloride, the urinary excretion of sodium and chloride steadily fell, and by December 1 the output in the urine both of sodium and of chloride was not much in excess of the intake of these ions. In other words, the metabolic response to the restriction of sodium chloride was very nearly like that which is

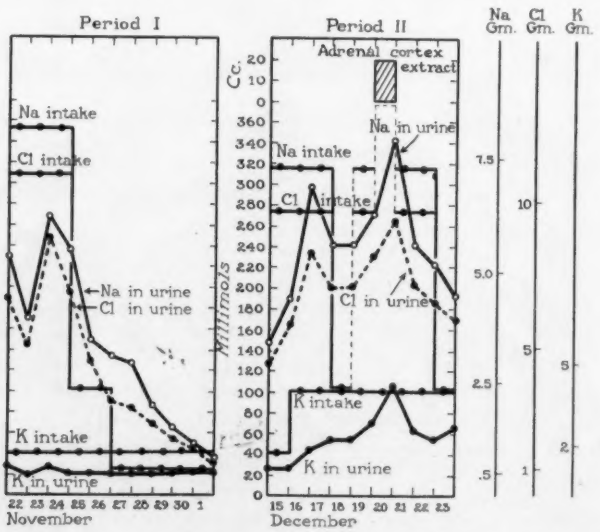

Chart 1 (case 1).—Metabolic studies of a patient with Addison's disease.

observed in health; namely, the excretion was diminished sufficiently so that a loss of sodium and chloride was avoided. A slight depression of the levels of the ions of sodium and chloride in the blood plasma and an increase of the potassium ions to a high normal level were noted.

In the interval from December 2 to December 15 the patient was given extra sodium chloride and sodium citrate by mouth daily. In addition, 10 cc. of extract of adrenal cortex [16] was injected on December 7 and again on December 8, the purpose of this being to insure as adequate body stores of sodium and chloride as may have existed on November 25. During this interval the intake of potassium was held at the low level of approximately 1.6 Gm. a day. The general condition of the patient became very satisfactory; certainly it was as good as before November 25. Beginning December 11 the sodium salts were administered by intravenous perfusions at twelve hour intervals so that changes could be made in the intake of salts without the patient's knowledge.

Observations from December 15 to 29 (metabolic data in table 1 and chart 1, period 2): From December 16 to 24, inclusive, 6.6 Gm. of potassium citrate was added to the perfusing fluids. This amount represented 2.4 Gm. of potassium and thus increased the daily intake of potassium from 1.6 to 4 Gm. The increased intake of potassium was followed immediately by a markedly increased excretion of both sodium and chloride. On December 18 the sodium salts were removed from the perfusing fluids, being replaced by dextrose, and the intake of sodium and chloride thus was reduced to the 6 Gm. of sodium chloride contained in the food and its seasoning. The excretion of sodium chloride continued high and by the morning of December 19, just twenty-four hours after the withdrawal of the extra sodium salts, the patient was definitely worse; she had lost 3 pounds (1.3 Kg.) and was very weak and sick.

On the evening of December 19 sodium chloride and sodium citrate were given by vein, and on December 20 the administration of sodium salts by mouth was resumed; also 20 cc. of adrenal cortex extract was administered.

On December 21 the patient was much improved, and on December 22 she was still strong.

On December 23 the sodium salts again were withdrawn, the intake of potassium continuing unchanged, and the following morning, December 24, the patient again was seriously weak and nauseated. The deleterious effect of these relatively small doses of potassium citrate being greatly in evidence, the observations were brought to a close.

The patient was restored to a satisfactory condition by the intravenous injection of sodium chloride and sodium citrate. The intake of potassium was diminished to the previous level of 1.6 Gm. a day, and after December 25 only 5 Gm. of extra sodium chloride and 2.5 Gm. of sodium citrate was given daily by mouth. On December 29 the patient was permitted to return to her home on this regimen.

In this case of Addison's disease of considerable severity the evidence indicates that a rigid restriction of sodium and chloride caused little disturbance of the metabolism of sodium and chloride and was reasonably well tolerated when the intake of potassium was low (1.6 Gm. a day) but that the addition of only 2.4 Gm. of potassium, as potassium citrate, provoked an increased excretion of sodium and chloride. Under these circumstances restriction of the intake of sodium and chloride precipitated symptoms of a crisis of Addison's disease. In the observation reported the addition of potassium citrate and the withdrawal of sodium salts were accomplished without the patient's knowledge, as all salts except the small amounts contained in the food were administered by intravenous perfusion. What appears in chart 1 to be a positive balance for sodium and chloride in period 2 of this experiment possibly is explained by the excretion of sodium and chloride in the feces. Analyses of the feces were not made.

CASE 2.—*Observations as to the Effect of the Level of Intake of Potassium on Addison's Disease; Also the Effect of Diuretic Drugs.*—The subject of this study was a woman 33 years old who, with the exception of diphtheria at the age of 3 years, a nervous breakdown at the age of 16 and rather frequent colds, was reasonably well until 1930. A severe infection of the upper respiratory tract,

called "flu," confined her to bed for a week in 1930, and from this she recovered very slowly. The body weight had been 148 pounds (67.1 Kg.) before, but it fell gradually, and the patient also lost endurance. She first noticed pigmentation of the face in 1933, which gradually involved the entire body. In 1935 a dentist called her attention to discoloration of the margins of the gums. Early in 1935 frequent attacks of hiccup, much nausea and anorexia and greatly increased weakness developed. During a menstrual period in July there were severe pains in the lower part of the abdomen. A physician was called. A diagnosis of Addison's disease was made, and treatment was started with daily injections of a commercial extract of adrenal cortex.[15] For some time before this the patient had craved salt and had used salt in place of sugar.

The patient first came to the clinic on July 19, 1935. She then was as dusky as a Negress and was deeply pigmented on the palms and fingers of the hands, over the bridge of the nose, around the mouth and at the points of pressure. The gingival margins also were pigmented. She was very weak and weighed 107 pounds (48.5 Kg.). The blood pressure was 114 mm. of mercury systolic and 72 diastolic. The pulse rate was normal. Roentgenograms revealed no evidence of tuberculosis of the lungs and no calcification in the region of the adrenal glands. The value for hemoglobin was 10.9 Gm. per hundred cubic centimeters. The flocculation test for syphilis was negative.

Under treatment with extract of adrenal cortex, sodium chloride and sodium citrate improvement was observed, and the patient soon said she felt as well as at any time after the onset of her illness. An attempt was made at this time to restrict the intake of sodium and chloride and to give only extract of adrenal cortex. This was only moderately successful, and when the administration of extract of adrenal cortex was discontinued, the sodium content of the blood serum fell from 313 to 282 mg. per hundred cubic centimeters, the urea content rose from 30 to 40 mg. and symptoms of crisis developed within forty-eight hours. The diet at that time probably contained about 4 Gm. of potassium.

After restorative treatment had been given the patient left for her home with instructions to take extract of adrenal cortex daily as well as 10 Gm. of extra sodium chloride and 1 level teaspoonful of sodium bicarbonate. At a visit to the office on September 26 she was stronger, her weight had increased to 115 pounds (52.1 Kg.) and she was free from symptoms. Her blood pressure was 115 mm. of mercury systolic and 70 diastolic. At another visit on November 8 she was feeling very well. Her blood pressure was 118 systolic and 72 diastolic. She had been able to work at household tasks.

On December 21 for no reason that was apparent at the time, symptoms of crisis developed suddenly: hiccup, nausea, vomiting, abdominal pain and great weakness. It is not improbable that the episode was precipitated by eating dates, figs, nuts and other "holiday foods" with a high content of potassium. More extract of adrenal cortex and more sodium chloride were given, but improvement was slow. The patient returned to the clinic on Jan. 16, 1936, and was placed in the hospital on that date.

Observations from Jan. 18 to Feb. 1, 1936 (metabolic data in table 2 and chart 2, period 1): A study was made of the effect of restricting the intake of sodium and chloride with the intake of potassium at a low level. On January 18 the diet was adjusted so that its estimated content of potassium was 1.6 Gm. The total intake of sodium chloride was made to approximate 16 Gm. a day, and sodium citrate was given in a daily dose of 5 Gm. The administration of extract of adrenal cortex was discontinued.

On January 20 the patient was comfortable, and the intake of sodium salts was reduced to the sodium chloride contained in the food and its seasoning (1.5 Gm. in the food and 4.5 Gm. used as seasoning). The patient became weaker, and on January 24 some hiccup, vomiting and abdominal pain occurred. On January 25 and 26 she was free from these symptoms but continued to be weak, and it was decided that the amount of salt required by the patient exceeded what she was receiving.[17]

During this period of seven days in which the intake of sodium chloride was restricted, the urinary excretion of sodium and chloride steadily diminished, and after the third day the output in the urine was less than the intake. On the other hand, the levels of sodium and chloride in the blood declined, and the urea content of the blood increased from 24 to 42 mg. per hundred cubic centimeters. The patient lost 1.2 Kg. in weight during the first three days but thereafter lost no more.

On January 27 the intakes of sodium and chloride were increased. Between January 30 and February 5 the condition of the patient was again entirely satisfactory.

Observations from February 6 to 14 (metabolic data in table 2 and chart 2, period 2): A study was made of the effect of increasing the intake of potassium. On February 6 the daily intake of potassium, which up to that time had remained at approximately 1.6 Gm., was increased to 4 Gm. by the administration daily of capsules of 6.6 Gm. of potassium citrate (2.4 Gm. of potassium). The administration of extra sodium chloride and sodium citrate was not interrupted. Nausea developed on the afternoon of the first day of administration of the extra amount of potassium. The next day, February 7, the face was drawn, and the patient was hiccuping. That night she was restless and sleepless. On February 8 the weakness had increased, and by the morning of February 9, after another sleepless night, the patient was extremely weak, and the respirations were irregular. A crisis was impending. The patient's weight had fallen from 47.7 to 45.6 Kg. in four days. The urinary excretion of sodium and chloride was markedly increased, the levels of sodium and chloride in the blood fell and a retention of potassium and urea was evident. The potassium content increased from 18.8 to 27.6 mg. per hundred cubic centimeters.[18]

On February 9 restorative treatment was administered. It consisted of the intravenous injection of large amounts of sodium chloride, sodium citrate and extract of adrenal cortex, and by February 15 the patient again felt well and had regained her lost weight.

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17. A later review of the record of this case gives the impression that the restriction of sodium and chloride between January 20 and 27 would have been tolerated better had the patient not been menstruating. Menstruation started on January 21 and continued until January 27. All the pain was pelvic. At no time did the clinical picture resemble that of an impending crisis. Thus the weakness never was such that the patient could not stand for her daily weighing. Her face did not look drawn, and the respirations never were of the hyperpneic type usually observed when a patient is in a serious condition.

18. This patient, receiving abundant sodium and chloride, reacted less stormily to the higher intake of potassium than the patients in cases 1 and 3, who had much smaller intakes of sodium and chloride. Unquestionably the high intakes of sodium and chloride protected her, but unquestionably the protection afforded was inadequate. The evidence is conclusive that potassium and potassium alone seriously aggravated her condition.

Observations from February 15 to 23 (metabolic data in table 2 and chart 2, period 3): A study was made of the effect of diuresis produced by the administration of ammonium nitrate and salyrgan. As considerable diuresis characteristically accompanies the development of symptoms of a crisis in patients with Addison's disease and since it accompanied the development of the critical con-

TABLE 2.

Date	Extract of Adrenal Cortex: Lot	Extract of Adrenal Cortex: Amount, Cc.	Intake: Sodium Chloride, Gm.	Intake: Sodium Citrate, Gm.	Intake: Total Sodium: Gm.	Intake: Total Sodium: Millimols	Intake: Total Chloride: Gm.	Intake: Total Chloride: Millimols	Intake: Total Potassium: Gm.	Intake: Total Potassium: Millimols	Intake: Total Nitrogen, Gm.	Twenty-Four Hour Urine: Volume, Cc.	Creatinine Nitrogen, Gm.	Total Nitrogen, Gm.	Sodium: Gm.	Sodium: Millimols	Chloride: Gm.	Chloride: Millimols	Potassium: Gm.	Potassium: Millimols	Sodium: Mg. per 100 Cc.
Jan. 1936																					Period 1.—Effect of Restricting Intake of Sodium a
18	..	..	16	5.0	7.27	317	9.75	275	1.6	41	7.2	2,330	0.26	5.06	6.69	291	9.29	262	1.45	37	314
19	..	..	16	5.0	7.27	317	9.75	275	1.6	41	7.2	2,060	0.32	6.04	6.69	291	9.25	261	1.54	39	...
20	..	..	6	...	2.37	103	3.65	103	1.6	41	7.2	1,900	0.31	6.66	6.53	284	8.63	244	1.33	34	312
21	..	..	6	...	2.37	103	3.65	103	1.6	41	7.2	2,460	0.27	5.87	5.08	221	7.18	202	1.44	37	...
22	..	..	6	...	2.37	103	3.65	103	1.6	41	6.9	1,400	0.29	6.05	3.52	153	4.90	138	1.27	33	334
23	..	..	6	...	2.37	103	3.65	103	1.6	41	4.9	620	0.28	6.08	2.08	90	3.15	89	1.16	30	300
24	..	..	6	...	2.37	103	3.65	103	1.6	41	5.7	450	0.20	4.56	1.18	51	1.83	52	0.74	19	...
25	..	..	6	...	2.37	103	3.65	103	1.6	41	6.2	535	0.25	5.75	1.49	65	1.13	32	0.95	24	...
26	..	..	6	...	2.37	103	3.65	103	1.6	41	6.9	900	0.20	4.96	1.48	64	2.41	68	0.95	24	...
27	..	..	11	2.5	4.83	210	6.72	189	1.6	41	5.2	1,300	0.29	7.05	2.48	108	3.75	106	1.53	39	288
28	..	..	11	2.5	4.83	210	6.72	189	1.6	41	6.8	860	0.23	5.76	2.55	111	3.46	98	1.44	36	...
29	..	..	21	7.5	9.77	423	12.80	360	1.6	41	6.4	795	0.28	6.06	2.79	121	4.03	114	1.77	45	...
30	..	..	16	5.0	7.27	317	9.75	275	1.6	41	6.8	1,010	0.24	5.53	2.75	120	3.81	107	1.24	32	286
31	..	..	16	5.0	7.27	317	9.75	275	1.6	41	7.2	1,100	0.25	4.70	3.01	131	3.83	108	1.19	30	...
Feb. 1	..	..	26	10.0	12.19	529	15.85	445	1.6	41	5.9	1,100	0.20	3.33	3.39	147	4.27	120	1.02	26	...
																					Period 2.—Effect of Increasi
2	..	..	16	5.0	7.27	317	9.75	275	1.6	41	5.5	1,100	0.27	2.99	3.32	144	4.57	129	0.97	25	...
3	..	..	16	5.0	7.27	317	9.75	275	1.6	41	...	1,440	0.26	2.97	3.74	163	5.16	146	0.85	22	318
4	..	..	16	5.0	7.27	317	9.75	275	1.6	41	7.1	630	0.25	2.48	3.36	146	5.37	155	0.92	24	...
5	..	..	16	5.0	7.27	317	9.75	275	1.6	41	7.1	740	0.26	2.57	3.64	158	4.54	128	0.93	24	316
6	..	..	16	5.0	7.27	317	9.75	275	4.0	103	5.4	1,060	0.26	2.84	4.00	174	5.43	153	1.15	29	...
7	..	..	16	5.0	7.27	317	9.75	275	4.0	103	6.2	2,280	0.24	2.81	6.84	297	8.17	230	1.90	49	...
8	..	..	16	5.0	7.27	317	9.75	275	4.0	103	7.2	1,690	0.24	2.61	6.82	297	8.10	228	2.44	62	330
9	72	20.0	36	15.0	17.10	745	18.70	585	1.6	41	6.7	1,210	0.21	2.24	4.75	207	5.74	162	2.23	57	366
10	72	10.0	26	10.0	12.19	529	15.85	445	1.6	41	6.2	1,660	0.28	3.52	4.76	207	7.30	206	4.56	107	...
11	..	....	16	5.0	7.27	317	9.75	275	1.6	41	6.7	640	0.19	1.84	1.74	76	2.79	79	1.26	32	...
12	77	5.0	16	5.0	7.27	317	9.75	275	1.6	41	7.1	800	0.26	1.99	2.11	92	3.32	94	1.13	29	...
13	77	5.0	16	5.0	7.27	317	9.75	275	1.6	41	6.7	1,660	0.27	2.96	2.46	107	3.82	108	1.14	29	...
14	81	5.0	16	5.0	7.27	317	9.75	275	1.6	41	6.9	1,760	0.28	2.60	3.07	134	4.10	116	0.84	22	...
																					Period 3.—Effe
15	..	...	16	5.0	7.27	317	9.75	275	1.6	41	6.5	1,760	0.27	2.59	4.19	182	5.61	158	0.94	24	321
16	..	3.0*	16	5.0	7.27	317	9.75	275	1.6	41	7.2	1,900	0.26	2.83	4.68	204	6.24	176	1.10	28	...
17	..	3.0*	16	5.0	7.27	317	9.75	275	1.6	41	6.4	2,285	0.27	3.24	4.66	203	6.32	178	1.16	30	...
18	..	4.5*	16	5.0	7.27	317	9.75	275	1.6	41	6.1	1,800	0.27	3.31	4.09	178	5.58	157	1.16	30	322
19	..	...	16	5.0	7.27	317	9.75	275	1.6	41	7.2	1,900	0.26	3.59	4.43	192	6.01	170	1.44	37	...
20	..	1.0†	16	5.0	7.27	317	9.75	275	1.6	41	7.0	1,630	0.26	3.01	5.00	130	4.40	124	1.09	28	...
21	..	...	16	5.0	7.27	317	9.75	275	1.6	41	...	1,830	0.28	3.15	5.37	155	5.35	157	0.91	23	...
22	..	...	16	5.0	7.27	317	9.75	275	1.6	41	...	1,770	0.25	2.80	3.35	146	4.70	133	1.15	29	...

* Ammonium nitrate, grams.
† Salyrgan, cubic centimeter.

dition in this case when potassium was administered and because such a loss of water alone might account for the loss of chloride and consequently for the symptoms, control observations were made in this third period after the administration on February 16, 17 and 18, respectively, of diuretic doses of ammonium nitrate. This salt provoked an increased volume of urine and the loss of 1.4 Kg.

of weight. Some nausea occurred, and on February 17 the breakfast was vomited; also, there was some increase in weakness but not enough to interfere with the patient's being up and about. On the morning of February 19 she said she felt very well. A loss of sodium chloride did not accompany the diuresis provoked by this administration of ammonium nitrate, and the concentrations of the electro-

ABLE 2.—*...ta in Case 2*

Blood Plasma										Blood Pressure, Mm. of Mercury		
Sodium		Chloride		Potassium								
Millimols	Mg. per 100 Cc.	Millimols per Liter	Mg. per 100 Cc.	Millimols per Liter	Mg. per 100 Cc.	Urea, Mg. per 100 Cc.	Sugar, Mg. per 100 Cc.	Carbon Dioxide, Vol. %	Body Weight, Kg.	Systolic	Diastolic	Clinical Observations
...dium ...oride, with Intake of Potassium at Low Level												
37	314	137	373	105	18.0	4.6	..	..	....	48.5	105	55	Began diet low in potassium
39	...	...	...	...	....	...	..	..	....	48.5	110	50	
34	312	136	366	103	19.1	4.9	24	85	46.2	48.5	105	45	
37	...	...	...	...	....	...	..	..	....	47.7	100	45	Weakness; menstruation began
33	308	134	351	99	21.4	5.5	24	94	46.1	47.8	105	50	Weaker; sleepless
30	306	130	346	98	19.7	5.0	30	98	50.0	47.5	110	40	Same
19	...	...	...	...	....	...	..	..	....	47.5	100	60	Vomiting and hiccup
24	...	...	...	...	....	...	..	..	....	47.7	100	60	Very weak
24	...	...	...	...	....	...	..	..	....	47.3	96	56	Same; still menstruating
39	283	124	317	89	21.3	5.5	42	95	47.5	47.0	96	50	Weaker
38	...	...	...	...	....	...	..	..	....	48.0	80	50	Improved; menses stopped
45	...	...	...	...	....	...	..	..	....	47.0	85	60	Stronger
32	288	125	327	92	20.1	5.1	..	..	....	46.7	80	60	No change
30	...	...	...	...	....	...	..	..	....	47.5	94	42	Stronger
26	...	...	...	...	....	...	..	..	....	47.7	98	56	No change
Increas... ...ake of Potassium													
25	...	...	...	...	....	...	..	..	....	48.4	94	44	No change
22	93	138	361	102	17.5	4.5	18	80	52.8	47.7	96	40	Doing well
24	...	...	...	...	....	...	..	..	....	47.7	92	44	No change
24	98	137	367	104	18.8	4.8	20	89	57.6	48.0	92	54	Looks and feels well
29	...	...	...	...	....	...	..	..	....	47.7	94	56	Walking more than usual
40	...	...	...	...	....	...	..	..	....	46.7	86	52	Weaker; haggard, hiccup
62	239	335	356	100	23.0	5.9	..	102	....	46.4	86	52	Great weakness; anorexia
57	304	342	356	100	27.6	7.1	27	..	....	45.6	84	50	Restorative treatment given
107	...	...	...	...	....	...	..	..	....	46.6	80	50	Much improved; slept well
32	...	...	...	...	....	...	..	..	....	47.0	85	45	Walked 6 blocks
29	...	...	...	...	....	...	..	..	....	47.7	80	62	
29	...	...	...	...	....	...	..	..	....	48.2	78	58	Appetite good
22	...	...	...	...	....	...	..	..	....	47.7	104	70	Doing well
3.—Effe... Diuretics													
24	22	140	374	106	17.2	4.4	14	86	53.8	47.7	92	54	No change
28	...	...	...	...	....	...	..	..	....	47.7	96	58	
30	...	...	...	...	....	...	..	..	....	47.3	90	52	Feels well, looks well
30	22	140	368	104	19.4	5.0	14	82	52.9	47.0	84	50	Weaker; some nausea
37	...	...	...	...	....	...	..	..	....	46.7	92	60	Tired, but up and about
28	...	...	...	...	....	...	..	..	....	46.3	94	60	Weak, but up and about
23	...	...	...	...	....	...	..	..	....	47.3	92	58	Feels well but tired
29	...	...	...	...	....	...	..	..	....	47.7	94	60	Feels very well

lytes of the blood were not altered. On February 20 1 cc. of salyrgan was administered intravenously. This also produced no ill effects.

On February 21 and 22 the patient felt very well, and on February 23 she was dismissed, with instructions to continue on the diet low in potassium and to take 10 Gm. of "extra" sodium chloride and 5 Gm. of sodium citrate daily.

In this case of Addison's disease of great severity a restriction of the intake of potassium to approximately 1.6 Gm. a day permitted limiting the sodium and chloride to the salt in the food and that used for its seasoning (6 Gm.) for a period of six days. In period 2 increasing the intake of potassium from 1.6 to 4 Gm. a day, by giving potassium as potassium citrate in capsules, precipitated a markedly increased urinary excretion of sodium and chloride and the rapid development of symptoms of a crisis of Addison's disease. This occurred despite the administration of extra sodium chloride and sodium citrate.

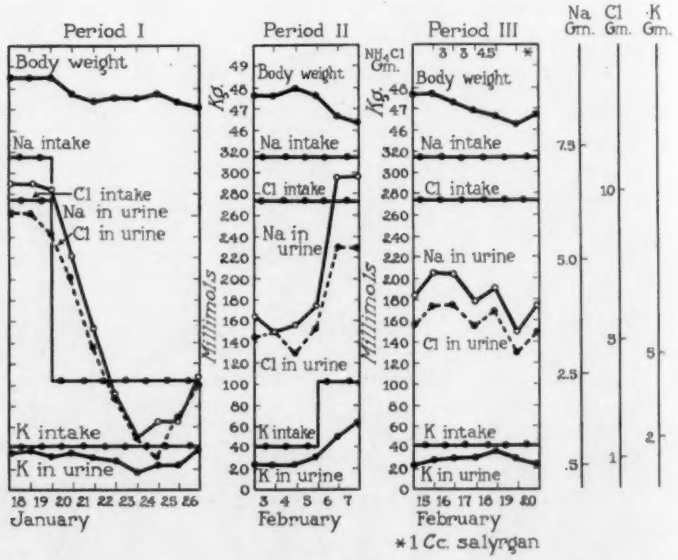

Chart 2 (case 2).—Metabolic studies of a patient with Addison's disease.

In period 3 the diuresis produced by the administration of ammonium nitrate was not accompanied with a loss of sodium and chloride or with the development of serious symptoms.

CASE 3.—*Observation on the Effect of the Level of Intake of Potassium in Addison's Disease.*—The subject of this study was a woman aged 37 who in 1913 had had an operation for acute tuberculous salpingitis and peritonitis. Signs and symptoms referable to Addison's disease developed in the autumn of 1933, consisting of fatigue, anorexia, loss of weight, a few black freckles and slight pigmentation of the gums.

When the patient was examined at the clinic in February 1934, Addison's disease was suspected, despite the absence of diffuse bronzing of the skin. Eight grams of "extra" sodium chloride was prescribed in the form of pills. This treat-

ment was reasonably effective, and at the time of a second visit, in September 1934, the condition of the patient was at least no worse than it had been.

The patient was placed in the hospital in September 1934. In order to settle any doubts about the diagnosis of Addison's disease, the salt pills were withheld, and the diet was made salt poor. Nausea and hiccup developed almost at once, and within two days the patient was in a state of collapse, with severe abdominal pain and cyanosis. Injecting sodium chloride and extract of adrenal cortex restored her, and she was then treated with extract of adrenal cortex without extra salt, the salt in the food amounting to approximately 6 Gm. The patient stood this for about three days, when she collapsed, so that restorative doses of sodium chloride again were needed. Later, while receiving treatment with extract of the anterior lobe of the pituitary gland, she tolerated restriction of sodium chloride for eight days,[19] as has been described before.[20]

The patient returned to her home, under continuous treatment with extract of adrenal cortex and extra sodium chloride, and remained well until about February 1. She was then brought to the hospital in impending crisis, which had developed following an attack of infection of the upper respiratory tract. Restorative treatment was administered, and the patient remained well until the period of observation reported here. She entered the hospital at our request on October 6. She had been receiving daily 3 cc. of extract of adrenal cortex by subcutaneous injection and 10 Gm. of sodium chloride and 1 level teaspoonful of sodium bicarbonate by mouth. Examination revealed no abnormality not previously noted, except some pigmentation of the skin of the knees and wrists and of the creases of the palms. Roentgenograms of the region of the adrenal glands did not reveal calcification.

Observations from October 6 to November 3 (metabolic data in table 3 and charts 3 and 4, period 1): A study was made of the effect of restriction of the intake of sodium and chloride with the intake of potassium at a low level. On October 6 the diet was made to contain approximately 1.6 Gm. of potassium and 6 Gm. of sodium chloride. In addition between October 6 and 15, 10 Gm. of sodium chloride and 5 Gm. of sodium citrate were given by mouth. The dose of extract of adrenal cortex was continued as before at 3 cc. a day.

On October 7 the sodium chloride in the blood serum measured 676 mg. per hundred cubic centimeters, the sugar 78 mg. and the urea 30 mg.

On October 16 the administration of "extra" sodium chloride and sodium citrate was discontinued, and the sodium chloride in the food was restricted to a maximum of not more than 1.5 Gm. a day. At the same time the dose of extract of adrenal gland was increased to 15 and later to 25 cc. a day. Menstruation commenced on October 18, and with it there was some cramping in the lower part of the abdomen, together with weakness and vertigo. Otherwise there were no untoward symptoms. On October 20, although menstruation was continuing, the unpleasant abdominal cramps had disappeared, and the patient looked and felt very well. She walked two miles. Her appetite was good. A week later, on October 27, she was still in good condition. Twelve days without trouble had

19. This experiment needs repeating in the light of our present knowledge of the importance of controlling the potassium content of the diet.

20. Wilder, R. M.: The Use of Anterior Lobe Pituitary Extract in the Treatment of Addison's Disease, Proc. Staff Meet., Mayo Clin. **9**:689-693 (Nov. 14) 1934.

then passed since the intake of sodium and chloride had been so rigidly restricted. During that time the sodium and chloride contents of the urine had decreased, as they would under similar conditions in the urine of a person in good health who had been deprived of sodium and chloride; thus the body stores of these elements were but little affected.

TABLE 3.—

	Intake										Twenty-Four Hour Urine									
	Extract of Adrenal Cortex				Total Sodium		Total Chloride		Total Potassium						Sodium		Chloride		Potassium	
Date	Lot	Amount, Cc.	Sodium Chloride, Gm.	Sodium Citrate, Gm.	Gm.	Millimols	Gm.	Millimols	Gm.	Millimols	Total Nitrogen, Gm.	Volume, Cc.	Creatinine Nitrogen, Gm.	Total Nitrogen, Gm.	Creatine Nitrogen, Mg.	Gm.	Millimols	Gm.	Millimols	Gm.	Millimols
Oct. 1935																				
13	47	3	16.0	5	7.27	317	9.75	275	1.6	41	7.0	1,080	0.26	5.03	..	4.18	181	5.21	147	0.95	24
14	47	3	16.0	5	7.27	317	9.75	275	1.6	41	6.6	1,570	0.30	5.34	..	5.94	258	6.77	191	1.06	28
15	52	15	16.0	5	7.27	317	9.75	275	1.6	41	6.4	1,430	0.29	5.37	..	5.95	258	7.79	220	1.25	32
												Period 1.—Effect of Restricting Intake of Sodium and								
16	52	15	1.5	..	0.59	26	0.91	26	1.6	41	6.2	1,940	0.29	4.95	..	5.35	232	7.43	210	1.52	39
17	52	15	1.5	..	0.59	26	0.91	26	1.6	41	6.6	2,650	0.28	4.68	..	4.11	178	5.88	166	1.00	26
18	52	25	1.5	..	0.59	26	0.91	26	1.6	41	6.4	2,180	0.28	4.55	..	2.93	127	4.09	115	0.87	22
19	52	25	1.5	..	0.59	26	0.91	26	1.6	41	6.2	1,360	0.25	3.34	..	2.01	88	2.73	77	1.01	27
20	52	20	1.5	..	0.59	26	0.91	26	1.6	41	7.0	1,290	0.30	4.99	..	1.43	62	1.65	47	0.87	22
21	52	20	1.5	..	0.59	26	0.91	26	1.6	41	6.4	1,520	0.27	4.89	..	0.97	42	1.35	38	0.79	20
22	52	10	1.5	..	0.59	26	0.91	26	1.6	41	6.4	1,480	0.28	5.60	..	1.03	45	1.32	37	0.72	18
23	52	10	1.5	..	0.59	26	0.91	26	1.6	41	6.4	1,870	0.27	5.14	..	1.20	52	1.33	37	0.65	17
24	52	10	1.5	..	0.59	26	0.91	26	1.6	41	6.4	1,710	0.27	4.81	..	1.36	59	1.69	48	0.73	19
25	52	10	1.5	..	0.59	26	0.91	26	1.6	41	6.4	1,495	0.26	4.23	..	1.13	49	1.55	44	0.81	21
26	52	10	1.5	..	0.59	26	0.91	26	1.6	41	6.4	1,610	0.25	3.94	..	1.15	50	1.29	36	0.53	13
27	52	10	1.5	..	0.59	26	0.91	26	1.6	41	6.4	1,680	0.30	4.70	..	1.19	52	1.78	50	1.23	31
28	..	..	1.5	..	0.59	26	0.91	26	1.6	41	6.4	1,410	0.29	4.66	..	1.00	44	1.26	35	0.92	24
29	..	..	1.5	..	0.59	26	0.91	26	1.6	41	6.4	1,790	0.25	4.38	..	1.49	65	1.43	40	0.69	18
30	..	..	1.5	..	0.59	26	0.91	26	1.6	41	6.4	1,720	0.26	4.91	..	2.02	88	2.23	63	1.16	30
31	..	..	1.5	..	0.59	26	0.91	26	1.6	41	6.4	2,040	0.28	5.24	..	2.02	88	2.28	64	1.16	30
Nov.																					
1	..	..	1.5	..	0.59	26	0.91	26	1.6	41	6.4	2,040	0.20	4.62	..	1.66	72	2.03	57	0.99	25
2	..	..	1.5	..	0.59	26	0.91	26	1.6	41	6.4	1,875	0.16	3.51	..	1.25	54	1.52	43	0.87	23
3	..	..	16.0	5	7.27	317	9.75	275	2.0	51	6.4	1,045	0.26	3.98	..	2.58	113	3.97	112	2.13	55
												Period 2—Effect of Increasing								
Jan. 1936																					
5	..	..	16.0	5	7.27	317	9.75	275	1.6	41	6.4	.....	....	....	..	....	...	....	...	....	..
6	..	..	16.0	5	7.27	317	9.75	275	1.6	41	6.4	.....	....	....	..	....	...	....	...	....	..
7	..	..	16.0	5	7.27	317	9.75	275	1.6	41	6.4	.....	....	....	..	....	...	....	...	....	..
8	..	..	16.0	5	7.27	317	9.75	275	5.8	148	12.8	1,050	0.25	4.86	6	5.13	223	7.96	224	1.36	35
9	..	..	15.2	5	6.97	302	9.26	260	5.8	148	12.0	2,120	0.29	5.83	..	7.32	317	10.78	304	2.53	56
10	..	..	15.2	5	6.97	302	9.26	260	5.8	148	12.0	1,595	0.28	6.86	..	9.73	423	14.61	412	3.14	81
11	52	3	16.5	5	7.48	326	10.10	284	5.5	141	12.8	1,445	0.27	6.74	..	8.60	374	13.66	385	3.52	90
12	52	10	16.5	5	7.48	326	10.10	284	5.5	141	11.7	2,116	0.31	9.99	99	9.27	404	13.82	390	4.14	106
13	52	20	1.5	..	0.59	26	0.91	26	5.5	141	10.9	1,775	0.29	9.76	81	7.93	345	10.74	304	3.80	97
14	52	20	35.0	5	14.77	642	21.40	600	1.6	41	6.6	1,760	0.20	7.89	..	4.08	178	6.47	182	3.29	85
15	71	10	16.0	5	7.27	317	9.75	275	1.6	41	4.8	.....	....	....	..	....	...	....	...	....	..
16	..	..	16.0	5	7.27	317	9.75	275	1.6	41	5.1	.....	....	....	..	....	...	....	...	....	..

* The specimen of urine reported on represents that passed from 7 a. m. to 7 p. m. on January 13, a twelve-hour period. The dition at 7 p. m., and 20 cc. more of extract of adrenal cortex was given after 7 p. m., with 800 cc. of a solution containing 16 Gm.

On October 28 the administration of extract of adrenal cortex was discontinued. On October 29 and 30 there were no symptoms. The patient's sleep during the night of October 30 and 31 was broken between 12 and 2 a. m. by restlessness. On October 31 weakness was increasing, and the appetite was lost. That night sleep was again broken by restlessness. Until then the patient had been up and about and had even been outdoors for short walks. On November

1 the patient rose, dressed and attended Sunday services in the building. She complained of weakness and noticed some pain in the epigastrium, some nausea and some deafness. These symptoms were minimal. The sodium and chloride contents of the blood plasma remained virtually unchanged, and the blood urea and serum potassium remained at normal values. On November 3 it was decided

Data in Case 3

Blood Plasma									Blood Pressure, Mm. of Mercury			
Sodium		Chloride		Potassium								
Mg. per 100 Cc.	Millimols per Liter	Mg. per 100 Cc.	Millimols per Liter	Mg. per 100 Cc.	Millimols per Liter	Urea, Mg. per 100 Cc.	Sugar, Mg. per 100 Cc.	Carbon Dioxide, Vol. %	Body Weight, Kg.	Systolic	Diastolic	Clinical Observations
...	...	...	...	....	...	..	..	....	57.0	100	68	Began diet low in potassium on October 8
...	...	...	...	....	...	..	..	....	57.5	90	56	
...	...	...	...	....	...	..	..	....	57.5	88	60	Hiccup
Chloride, with Intake of Potassium at Low Level												
325	142	391	110	17.9	4.6	22	..	54.1	57.5	100	60	Began diet low in sodium
...	...	...	...	....	...	..	..	....	56.6	94	60	No complaints
318	138	371	104	16.3	4.2	..	..	54.0	55.9	100	78	Menstruating
316	137	371	104	17.3	4.4	20	..	58.0	55.9	84	58	Much stronger; walked 2 miles
...	...	...	...	....	...	..	..	....	55.0	90	66	No complaints
315	137	373	105	....	...	26	..	54.8	55.1	104	68	
...	...	...	...	....	...	..	..	....	55.2	90	70	Went shopping
...	...	...	...	....	...	20	..	55.0	55.2	100	70	
308	134	365	102	....	...	..	..	....	55.2	94	68	
316	138	366	103	19.1	4.9	16	70	67.0	55.0	90	70	Looks well
...	...	...	...	....	...	..	..	....	55.0	92	60	
...	...	...	...	....	...	..	..	....	55.0	86	60	Weaker
311	135	362	102	17.9	4.6	24	..	58.0	55.0	86	52	Walked 2 miles
314	136	362	102	17.8	4.6	22	..	56.0	55.2	90	58	Very well
312	135	361	102	17.5	4.5	22	70	52.2	54.8	90	64	Weaker
313	136	363	103	19.5	5.0	27	76	54.0	54.5	90	54	Restless
315	137	357	101	16.9	4.3	24	77	54.0	54.1	80	64	Weaker; hiccup
306	133	344	97	15.5	4.0	26	79	53.0	53.9	82	50	Weaker
...	...	...	...	....	...	..	..	....	55.9	78	50	Very well
Intake of Potassium												
...	...	...	...	....	...	..	..	....	....	98	54	Treatment unchanged since last visit; patient very well
312	136	371	104	15.3	3.9	22	..	50.4	55.7	78	54	
312	136	376	106	16.2	4.2	22	..	51.3	55.7	78	62	
311	135	373	105	16.2	4.2	22	..	46.6	55.7	74	64	
309	134	378	105	20.2	5.2	27	..	48.5	56.0	88	64	Diarrhea (6 stools)
...	...	...	...	....	...	..	..	....	55.5	88	56	Diarrhea (15 stools)
311	135	365	103	22.7	5.8	34	..	48.5	55.3	90	72	Very weak
...	...	...	...	....	...	..	..	....	55.0	90	58	Verk weak; depressed
301	130	350	99	26.9	6.9	54	86	46.5	54.2	90	54	Crisis; treated*
...	...	...	...	....	...	..	..	....	55.3	90	50	Improved
...	...	...	...	....	...	..	..	....	56.0	88	48	No complaints
326	142	391	110	16.9	4.3	..	..	....	56.5	94	60	Condition excellent

figures should be multiplied by 2 for comparison with previous twenty-four hour collections. The patient was in a critical co of sodium chloride and 4 Gm. of sodium citrate.

to resume the previous treatment with sodium chloride and sodium citrate, although the experiment could doubtless have been continued longer.

On November 3 the patient was permitted to go home, where she continued in good condition without having to resort to injections of extract of adrenal cortex except for a few days in December after an infection of the upper respiratory tract. Her diet was adjusted so that the intake of potassium did not exceed

2.0 Gm. a day, and she was allowed 10 Gm. of sodium chloride and 5 Gm. of sodium citrate a day by mouth. She felt well and was able to do her housework. She returned to the hospital at our request on Jan. 5, 1936.

Observations from Jan. 5 to 17, 1936 (metabolic data in table 3 and charts 3 to 5, period 2): A study was made of the effect of increasing the intake of potassium in the food. From January 5 to 7, inclusive, the diet was adjusted so that the intake of potassium did not exceed 1.6 Gm. a day. Extra sodium chloride and sodium citrate were administered by mouth. This regimen approximated that to which the patient had been adhering for the preceding two months.

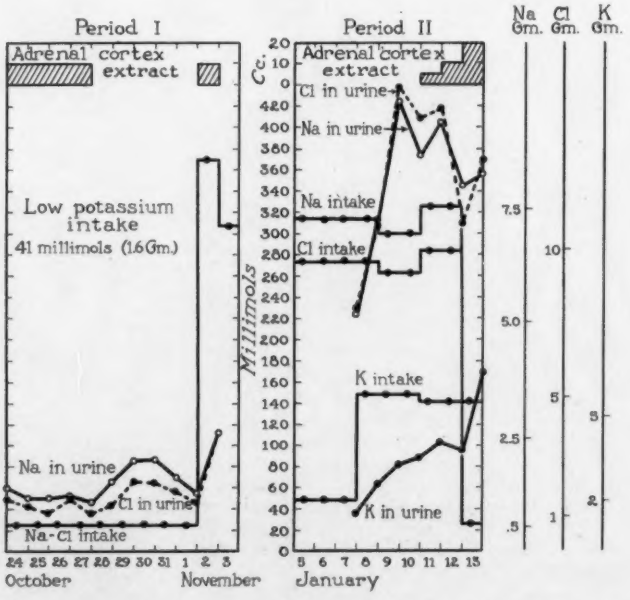

Chart 3 (case 3).—Metabolic studies of a patient with Addison's disease.

On January 8 the level of the intake of potassium was increased to 5.8 Gm. a day. This was accomplished by the inclusion in the diet of foods rich in potassium. Within twenty-four hours significant disturbances were observed in the urinary excretion of sodium and chloride and in the level of the sodium and chloride in the blood. The excretion of sodium and chloride increased. Diarrhea occurred on January 10 and 11. It was arrested by a dose of bismuth subnitrate and by arranging the diet so that it contained less laxative foods. This reduced the intake of potassium to 5.5 Gm. a day. It was suggested that the high intake of potassium was responsible for the diarrhea, the symptom having been observed occasionally in adrenalectomized dogs. Extract of adrenal cortex was given in small doses beginning on January 11.

On January 11, although the diarrhea had stopped, the patient was weak. On January 12 she felt as sick as she had at any time in the period from Oct. 16

to Nov. 3, 1935, although on Jan. 11 and 12, 1936, she was receiving sodium salts in large doses and extract of adrenal cortex in a small dose, and from Oct. 15 to Nov. 3, 1935, the intake of sodium and chloride were restricted to a minimum, and after October 27 she received no extract of adrenal cortex. She complained on January 13 of a great loss of strength, of deafness and of epigastric distress. She was apprehensive and depressed. On January 13 the "extra" sodium chloride and sodium citrate were withheld, the total intake of sodium and chloride being reduced to that contained in the food. Anorexia prevented the patient from eating much of the food. At 1:10 p. m., after the noon meal, an episode of hiccupping occurred which lasted for ten minutes. At 3 p. m. the patient tried to walk but could not stand. At 7:30 p. m. she was very weak and was failing

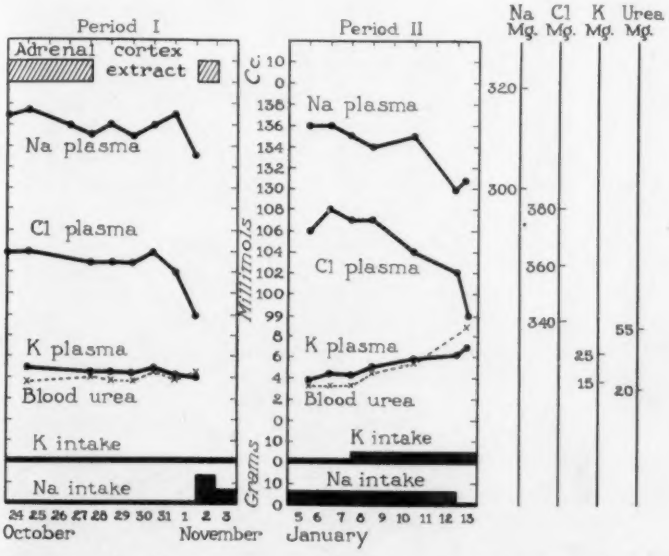

Chart 4 (case 3).—Further metabolic studies of a patient with Addison's disease.

rapidly. The respirations were hyperpneic, the radial pulse was palpated with difficulty and the patient looked haggard. Between 7 a. m. and 7 p. m. she had passed nearly 2,000 cc. of urine, and her body weight had declined 2 pounds (0.9 Kg.), it being 4 pounds (1.8 Kg.) less than on January 9. A crisis obviously impended, and restorative treatment therefore was necessary that evening. A solution containing 16 Gm. of dextrose, 16 Gm. of sodium chloride, 4 Gm. of sodium citrate and 20 cc. of extract of adrenal cortex was administered.

On January 14 the patient felt well until in the afternoon, when again she had some symptoms of adrenal insufficiency. Another intravenous injection was given. Her condition then was good, and by January 17 the lost weight had been regained and she could be permitted to return to her home.

In this case of Addison's disease of moderate severity the evidence is conclusive of intolerance to potassium and benefit by limiting the

intake of it. In the period elapsing from Jan. 5 to 14, 1936, when the food provided from 5.5 to 5.8 Gm. of potassium, large losses of sodium, chloride and nitrogen occurred, together with marked creatinuria (charts 3 to 5). This occurred despite a large intake of sodium and chloride and the administration of small doses of extract of adrenal cortex. In an earlier period, from Oct. 27 to Nov. 6, 1935, when the diet was so constructed that the daily intake of potassium did not exceed 1.6 Gm., the patient tolerated an almost complete deprivation of sodium and chloride for a period of seventeen days. Extract of adrenal cortex was administered during the first twelve days of this period but not during the last five.

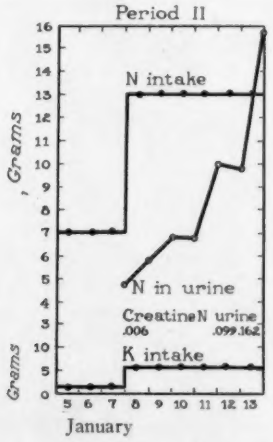

Chart 5 (case 3).—Further metabolic studies, period 2.

Of significance also is the fact that with a diet low in potassium and only moderate doses of extra sodium and chloride, the patient remained in good health at home for sixty-six days without the benefit of injections of extract of adrenal cortex, which previously, when attention was not directed to the potassium content of the diet, had been necessary.

The ill effect of the larger intake of potassium from Jan. 8 to 13, 1936, inclusive, is not attributable to diuresis. The amount of water excreted daily was not more than that excreted between Oct. 16 and Nov. 3, 1935, when the intake of potassium was lower. The correlation is with the urinary excretion of sodium and chloride—in the periods when the intake of potassium was low the excretion did not greatly exceed the intake of sodium and chloride; in the period when the intake of potassium was high it did.

COMMENT

That potassium is toxic when perfused through the isolated heart or other muscles or when injected in sufficient amounts into an intact animal is a matter of common knowledge. Also that the kidney of a patient with adrenal insufficiency is relatively less competent than normal has been known since its demonstration in 1916 by Marshall and Davis.[21] Hastings and Compere [22] in 1931 showed that the concentration of potassium in the blood of dogs increases after the removal of the adrenal glands. The concentration before death reached 20 millimols per liter, a value which was found to be comparable to the concentration of potassium in the blood of normal dogs killed by the injection of a large amount of potassium. Their statement that this observation "might be of importance in reaching an understanding of the cause of death following the functional or surgical removal of the suprarenal glands" proves to have been prophetic.

Concentrations of plasma potassium as great as those recorded by Hastings and Compere have not been encountered among patients with Addison's disease, but that retention of potassium may occur in Addison's disease has been shown by Loeb and others.[23] In twenty-four cases Marañón and Collazo [24] used Kramer's method of analysis and obtained values ranging from 21.7 to 49.5 mg. per hundred cubic centimeters (5.5 to 12.7 millimols per liter). The normal concentration of potassium in the plasma is from 16 to 20 mg. per hundred cubic centimeters (4 to 5 millimols per liter). The Spanish investigators attributed the dehydration of Addison's disease to a disturbance of equilibrium between the potassium and the sodium of the plasma and made the suggestion that one of the physiologic activities of the hormone of the adrenal cortex is the maintenance of this regulation. This equilibrium is not easily disturbed. If one adrenal gland remains intact, as was shown by Loeb, Atchley, Benedict, and Leland,[1] large doses of potassium salts may be given without harm. In one experiment from 5 to 7 Gm. of potassium chloride was administered daily to a dog deprived of one adrenal gland, with the purpose of inducing an increased excretion of sodium. No loss of sodium occurred, and the proportions of potassium and sodium in the plasma remained unchanged.

21. Marshall, E. K., Jr., and Davis, D. M.: The Influence of the Adrenals on the Kidneys, J. Pharmacol. & Exper. Therap. **8**:525-550 (Sept.) 1916.

22. Hastings, A. B., and Compere, E. L.: Effect of Bilateral Suprarenalectomy on Certain Constituents of the Blood of Dogs, Proc. Soc. Exper. Biol. & Med. **28**:376-378 (Jan.) 1931.

23. Loeb, R. F.: Chemical Changes in the Blood in Addison's Disease, Science **76**:420-421 (Nov. 4) 1932.

24. Marañón, G., and Collazo, J. A.: Die Deshydrierung in der Addisonschen Krankheit und ihr Mechanismus, Wien. Arch. f. inn. Med. **27**:189-200, 1935.

Urechia and his collaborators [25] suggested that the toxicity of the potassium ion and its action on muscle fiber explain the asthenia of Addison's disease, and Nicholson and Soffer [26] obtained a striking correlation between the concentration of potassium in the plasma of adrenalectomized dogs and the auricular fibrillation not infrequently encountered after adrenalectomy. The value for potassium in the animals in which fibrillations developed was never less than 52 mg. per hundred cubic centimeters (13.3 millimols per liter), and in one animal it reached 92.5 mg. per hundred cubic centimeters (23.6 millimols per liter). Auricular fibrillation has not been recorded in Addison's disease, but probably it has been looked for infrequently in the terminal stages, when the retention of potassium is at its maximum.

Harrop and his associates [27] (1933) also considered the extreme muscular weakness of adrenalectomized dogs to be due in part to the disturbance in the relative concentration of the basic ions in the tissue and body fluids and observed further that adrenalectomized dogs maintained with an extract of adrenal cortex and fed exclusively on meat (a food rich in potassium) were unusually sensitive to withdrawal of the extract. Harrop and his co-workers have also pointed out that the consequence of the loss of sodium chloride and water through the kidneys of adrenalectomized dogs recalled the studies of Gamble and his associates on dogs which had lost sodium chloride and water by drainage of pancreatic juice from a Pavlov fistula: "The greater rapidity of the appearance of serious symptoms on a meat diet without added salt, in which the fixed base is in large part potassium, and hence unsuited to the repair of plasma and the interstitial fluid loss was striking and also in keeping with the effects in suprarenalectomized dogs deprived of extract." Gamble and McIver in one of their papers commented on an earlier observation of Pavlov that a milk diet will considerably prolong the survival period of dogs suffering from a deficit of sodium resulting from a pancreatic fistula.

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25. Urechia, C. I.; Benetato, G., and Retezeanu: Le potassium sanguin après extirpation des glandes surrénales, Compt. rend. Soc. de biol. **119**:439-440 (March 21) 1935.

26. Nicholson, W. M., and Soffer, L. J.: Cardiac Arrhythmia in Experimental Suprarenal Insufficiency in Dogs, Bull. Johns Hopkins Hosp. **56**:236-243 (April) 1935.

27. Harrop, G. A.; Weinstein, Albert; Soffer, L. J., and Trescher, J. H.: The Diagnosis and Treatment of Addison's Disease, J. A. M. A. **100**:1850-1855 (June 10) 1933. Harrop, G. A.; Saffer, L. J.; Ellsworth, Read, and Trescher, J. H.: Studies on the Suprarenal Cortex: III. Plasma Electrolytes and Electrolyte Excretion During Suprarenal Insufficiency in the Dog, J. Exper. Med. **58**:36 (July) 1933.

Our idea that limiting the intake of potassium might favorably influence the course of Addison's disease thus was a rational deduction from indirect evidence already available.

We are fully aware that the data of the present report are not as complete as might be desired. Analyses of the feces should have been made. More determinations of the excretion of creatine would have been helpful, and longer periods between changes of regimen would have been advantageous. It happened that the facilities of the laboratory at the time did not permit more extensive analytic determinations, and the necessary consideration of the welfare of the patients frequently interfered with the extension of the periods of observation. The data,

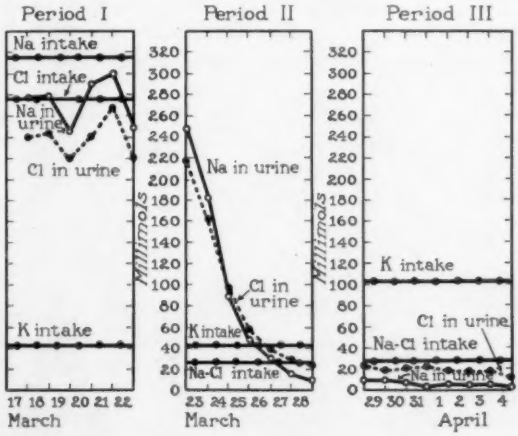

Chart 6.—Metabolic studies of a normal subject.

however, are sufficiently complete to reveal that low levels of intake of potassium are advantageous in Addison's disease, and this was the primary question for which we sought an answer. An intake of potassium not greater than that provided by a general diet (about 4 Gm.) caused a loss of ions of sodium and chloride and the development of symptoms of crisis even when "extra" sodium chloride and sodium citrate were administered. A diet still higher in its content of potassium (period 2 in case 3) was correspondingly more disturbing and produced serious consequences which were not prevented even by treatment with "extra" sodium chloride, sodium citrate and small doses of extract of adrenal cortex. On the other hand, diets restricted in the content of potassium to approximately 1.6 Gm. permitted the maintenance of all three patients without resort to injections of extract of adrenal cortex,

and under such circumstances even a rigid restriction of the intake of sodium salts was tolerable (cases 1 and 3) for a period of many days.

That potassium in the maximal amounts received by these patients produces no untoward effects in normal subjects is perfectly obvious. The amounts involved are no greater than most persons receive each day with their usual meals. A series of observations on a normal subject comparable to those made with the patient in case 2 will be reported soon by two of us (Drs. Kepler and Adams) with Dr. Blum. The data of three periods of their study are shown in chart 6. It is clearly evident from them that increasing the intake of potassium from a low to a high level provoked no loss of sodium and chloride ions even when the intake of sodium and chloride was at a minimum. The feces were analyzed in their study, and since the observations were made in the winter, when the loss of sodium and chloride through the skin is at a minimum, the metabolic balances for sodium and chloride were perfectly reliable.

We have limited the evidence for reporting here to that obtained in only three cases of Addison's disease, because in these cases the metabolic data available were reasonably complete; our conclusions, however, are supported by additional experience. Recently a patient was placed in the hospital for withdrawal of salt from the diet, a procedure which Harrop and his associates proposed as a diagnostic test for adrenal insufficiency. It consists of restricting the intake of sodium and chloride to the salts of the unseasoned foods and has been supposed not to be tolerable for longer than a few days (five at the most) in any case of Addison's disease. The patient in question was not grossly pigmented, and her only symptom was weakness. She withstood the procedure for six days; no symptoms other than the original weakness developed and there were no greater changes for the values of sodium and chloride of the plasma than would be normal. At a later time, with a diet made to contain approximately 5.5 Gm. of potassium, the test was repeated. It was badly tolerated, and clear symptoms of adrenal insufficiency developed within three days. It now is apparent that attention must be paid to the potassium content of the diet in evaluating the results of this diagnostic procedure and likewise that all earlier experimental work on adrenal insufficiency, as well as procedures for the biologic assaying of extracts of adrenal cortex, will require revision from the standpoint of rigid control of the intake of potassium.

Two patients with obvious Addison's disease recently were admitted to the hospital in conditions bordering on crisis. In both cases the urea content of the blood and the potassium content of the plasma were elevated, whereas the sodium and chloride contents of the plasma were moderately depressed. In these cases, without resorting to injections of

extract of adrenal cortex but by restricting the intake of potassium and adequately supplying calories, sodium chloride and sodium citrate, the patients were restored.

It must be emphasized that subjects who are eating little or nothing because of nausea, are subsisting, in fact, on a metabolic mixture of food material high in potassium. This is because the endogenous supply of nutrients, on which they are depending, contains a large amount of tissue protein, which, like meat, is rich in potassium. Wastage of protein is characteristic of the crisis of Addison's disease, as is evidenced by negative nitrogen balances, and it is not improbable that the well known advantage of injections of dextrose in the treatment of the crises of Addison's disease depends, in part at least, on the "sparing effect" on protein of the calories supplied by the dextrose.

Diets Low in Potassium.—The preparation of a palatable diet which will contain not more than 1.6 Gm. of potassium requires the same careful planning as does that of a diet for a diabetic patient. Sherman's table showing the ash constituents of foods in percentage of the edible portion was compiled from various sources, and, while we have followed it to date in planning these diets, we are far from satisfied with it. A recent study by Davidson and LeClerc [28] indicated that there is a considerable variation in the content of potassium and other bases of vegetables obtained from different regions and that the mineral composition of vegetables seems to be correlated with the fertilizer treatment of the soil or the chemical composition of the irrigation water. Possibly also the meat of animals grazing on fields fertilized with potassium will be richer in potassium than the meat of other animals. These matters are being investigated by Sister Mary Victor and Miss Lydia Nelson, graduate students in nutrition of the Mayo Foundation. A practical suggestion already has come from the study being made by Sister Mary Victor—by boiling vegetables in two or three changes of water from 75 to 80 per cent or more of their salts, including potassium, can be removed. Potatoes, for instance, which normally contain more than 400 mg. of potassium in each hundred grams, can be washed by this means and subsequently seasoned by the addition of table salt. Foods especially rich in potassium, containing, for example, more than 300 mg. of potassium in each hundred grams, include the following: meats, fowl, fish of all kinds, potatoes, sweet potatoes, peas, beans, beets, cabbage, celery, chard, chestnuts, spinach and other greens, pumpkin, squash, parsnips, dried fruits (especially dates), figs, prunes, banana, pineapple,

28. Davidson, J., and LeClerc, J. A.: The Variation in the Mineral Content of Vegetables, J. Nutrition **2**:55-66 (Jan.) 1936.

nuts of all kinds, wheat, bran and molasses. Obviously such foods must be used in moderation if the total intake of potassium is to be held below 1.6 Gm.

The diet planned by Sister Mary Victor for the experiments here reported was as follows:

LOW POTASSIUM DIET

Potassium, 1.6 Gm.; Protein, 57 Gm.; Calories, 2,350

Food	Grams	Approximate Measure
Breakfast		
Orange juice	100	½ glass
Cornflakes	15	1 serving
Egg	50	One
Bread	50	2 slices
Butter	20	2 squares
Cream, 40 per cent fat	75	⅜ cup
Coffee if desired		
Dinner		
Beef tenderloin (weight uncooked)	70	1 average serving
Potato, thrice boiled	100	1 average serving
Carrots	25	1 small serving
Celery	25	2 celery hearts
Grapefruit	55	4 sections
Bread	50	2 slices
Butter	25	2½ squares
Cream, 40 per cent fat	20	1 tablespoon
Tea or coffee if desired		
Supper		
Cheese	40	2 cubic inches
Rice (weight dry)	25	1 average serving
Tomato	50	½ average serving
French dressing	15	1 tablespoon
Apple	80	¾ average size
Bread	50	2 slices
Butter	25	2½ squares
Cream, 40 per cent fat	20	1 tablespoon
Tea or coffee if desired		

This diet, and indeed all the diets low in potassium that we have been able to plan, contain what seems to be an adequate amount of protein but a bare minimum of calcium and other minerals. The content of vitamins A and C is adequate, but the content of vitamins B and G is low. An important consideration therefore will be the matter of supplementing such diets with what is missing. This can be accomplished by prescribing calcium phosphate, an iron salt and a suitable concentrate of vitamins B and G.

CONCLUSIONS

The potassium content of the diet of patients with Addison's disease affects the course of the disease and the development of the symptoms of crisis.

An intake of potassium not greater than 4 Gm. a day, an amount comparable to that contained in a normal diet, may promote the excretion of sodium and chloride whereby significant losses of sodium and chloride occur and symptoms of crisis are precipitated. It may not be possible to prevent the occurrence of these effects of potassium with intakes of sodium and chloride as high as those provided by the administration of 18 Gm. of sodium chloride and 5 Gm. of sodium citrate daily.

If the intake of potassium is restricted to about 1.6 Gm. a day, the requirement of sodium and chloride is materially diminished, and it becomes possible, although not necessarily desirable, to maintain patients with smaller doses of sodium salts than otherwise are needed and without injections of extract of adrenal cortex. Optimal therapeutic results demand not only the restriction of potassium but optimal rather than minimal doses of sodium salts and when possible, and certainly in emergencies, injections of an active extract of adrenal cortex.

The arranging of a diet which will contain not more than 1.6 Gm. of potassium requires careful planning. Such a diet is likely to be inadequate in calcium, phosphate, iron and vitamins B and G. To avoid complications from deficiencies of these factors, the diet should be supplemented suitably by the addition of calcium phosphate, some iron salt and a concentrate of vitamins B and G.

ENDEMIC PNEUMONIA

PNEUMOCOCCIC TYPES AND THEIR VARIATIONS IN INCIDENCE AND MORTALITY FOR ADULTS AND CHILDREN

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Classification of the types of pneumococci in endemic pneumonia was incomplete previous to and during the earliest part of our work. Originally group IV contained types IV to XXXII, and at least three different specific types were included in type II and two in type III. Since the more comprehensive classification of Cooper [1] and her co-workers has been accepted, the distribution of the types of pneumococci in endemic pneumonia has been studied in various parts of the world. These types have occurred in differing proportions, according to reports published in New York,[2] Boston [3] and San Francisco [4] and in Great Britain,[5] Germany,[6] Holland,[7] India [8] and South Africa.[9]

This study received financial support in part from the Metropolitan Life Insurance Company.

From the Littauer Pneumonia Research Fund of the New York University College of Medicine; from the Medical Service, the Harlem Hospital (Department of Hospitals), and from the Research Laboratories (Department of Health) of the City of New York.

1. Cooper, G.; Edwards, M., and Rosenstein, C.: The Separation of Types Among the Pneumococci Hitherto Called Group IV and the Development of Therapeutic Antiserums for These Types, J. Exper. Med. **49**:461-474 (March) 1929. Cooper, G.; Rosenstein, C.; Walter, A., and Peizer, L.: The Further Separation of Types Among the Pneumococci Hitherto Included in Group IV and the Development of Therapeutic Antiserums for These Types, ibid. **55**:531-554 (April) 1932.

2. Bullowa, J. G. M.: The Reliability of Sputum Typing and Its Relation to Serum Therapy, J. A. M. A. **105**:1512-1518 (Nov. 9) 1935. Raia, A.; Plummer, N., and Shultz, S.: New Types of Pneumococci in the Pneumonias of Children, Am. J. Dis. Child. **42**:57-68 (July) 1931.

3. Heffron, R., and Varley, F.: A Study of Lobar Pneumonia in Massachusetts: Methods and Results of Pneumococcus Type Determination, 1931-1932, Am. J. Pub. Health **22**:1230-1248 (Dec.) 1932.

4. Kohl, C., and Reitzel, R. J.: Type Specificity in Pneumonia and Pneumococcic Infection, J. A. M. A. **106**:1557-1561 (May 2) 1936.

(Footnotes continued on next page)

We have studied the 4,048 cases of endemic pneumococcic infection recorded during seven years, 1928 to 1935, at the Harlem Hospital. There were 2,708 cases of pneumonia in adults and 663 cases of pneumonia (primary) in children, a total of 3,371 cases.[10] In addition, there were 573 cases of adults and 204 cases of children suffering from bronchitis or acute infection of the upper respiratory tract, which in some instances simulated pneumonia when the patient was admitted to the hospital.

The methods of study have been outlined in our studies on bacteremia.[11] In addition to the methods used for adults, the sputum of many of the children was obtained by means of the laryngoscope and in some cases by gastric aspiration. In most cases, however, pharyngeal swabbing, with incubation of the swab in broth, was carried out.

The patients were admitted to the Harlem Hospital to the service for patients with acute respiratory diseases of one of us (Dr. Bullowa) or to the pediatric service of Dr. Morris Gleich, who granted permission for the study of the children with pneumonia. The Harlem Hospital is a general municipal hospital located in the northeastern section of Manhattan Island, in the center of a population of about 250,000 Negroes. The district reached by ambulance includes also a large population of Puerto Ricans, Italians, Finns and Irish. The ambulance service is active, and according to the terms of the city charter it may not be refused to any patient who demands hospitalization. Patients are occasionally transferred to or from other hospitals. Accordingly,

5. Cowan, J. M., and others: Felton's Serum in Lobar Pneumonia, Lancet **2**:8-11 (July 2) 1932. Cruickshank, R.: Felton's Serum in Lobar Pneumonia: Serological Typing of Pneumonia, Tr. Roy. Med.-Chir. Soc. Glasgow **25**:34-38, 1931.

6. Gundel, M., and Schwarz, F. K.: Ueber die Typendifferenzierung und Epidemiologie der Gruppe X der Pneumokokken, Ztschr. f. Hyg. u. Infektionskr. **113**:498-522, 1932.

7. Vedder, A.: Das Vorkommen der Pneumokokkentypen 4-32 in Amsterdam, Acta brev. Neerland. **3**:35-37, 1933.

8. Napier, L. E., and Dharmendra: Incidence of Pneumococcal Types in Pneumonia in Assam, Indian M. Gaz. **70**:181-185, 1935.

9. Lister, S., and Ordman, D.: The Epidemiology of Pneumonia on the Witwatersrand Gold Fields and the Prevention of Pneumonia and Other Allied Acute Respiratory Diseases in Native Laborers in South Africa by Means of Vaccine, Publication 37, South African Institute for Medical Research, 1935, vol. 7.

10. Only cases of pneumonia due to a single classified pneumococcus have been included in our graphs and tables. Cases were omitted in which a second pneumococcus or other organism complicated the designation as well as cases of pneumonia due to an unclassified pneumococcus. The latter constituted 1.2 per cent of the cases of pneumococcic pneumonia recorded during the last four years.

11. Bullowa, J. G. M., and Wilcox, C.: Incidence of Bacteremia in the Pneumonias and Its Relation to Mortality, Arch. Int. Med. **55**:558-573 (April) 1935.

one may say that the material included in the statistics is a random sample of the cases of pneumonia as they occurred from year to year and represents the endemic pneumonia and pneumococcic infections of the northern half of Manhattan Island and the lower portion of the Bronx.

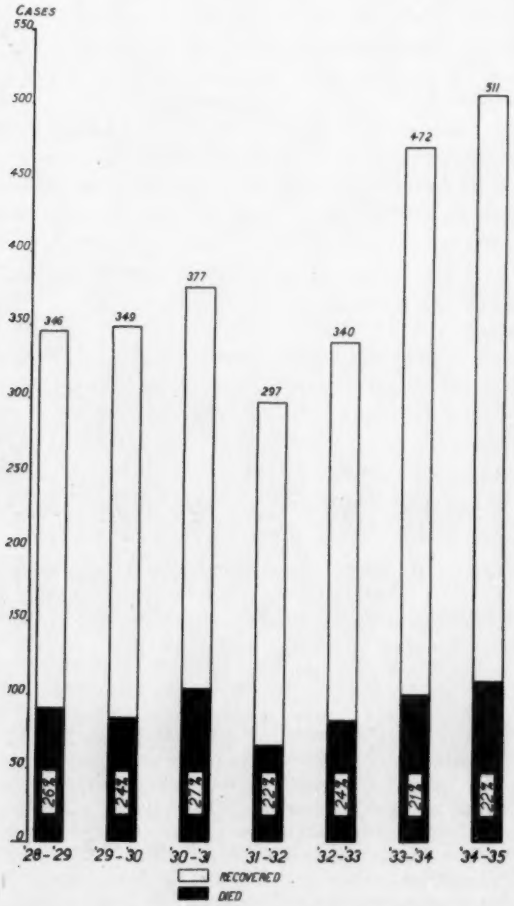

Chart 1.—Summary of 2,708 cases of pneumococcic pneumonia in adults from 1928 to 1935. In charts 1 and 2 the black columns represent the patients who died and the white columns the patients who recovered.

The statistical year runs from July 1 to June 30, thus including an entire pneumonia season. The total number of patients admitted to the hospital year by year, together with the mortality percentages, is

graphically presented in charts 1 and 2. It will be observed that the mortality for adults varied from 24 to 27 per cent in the first three years, and in the four later years it varied from 21 to 24 per cent. During this period the mortality for children varied from 7 to 12 per cent in five of the seven years studied but reached 16 per cent in 1930-1931 and 20 per cent in 1932-1933. The year 1930-1931, which showed a high death rate (16 per cent) for children. showed also a very high death rate for adults (27 per cent). In 1932-1933, when there were fewer cases in children, there was a high mortality for children (20 per cent). Previously and subsequently it did not exceed 16 per cent. There were a large number of cases of Streptococcus haemolyticus infection complicating pneumonia in the year 1930-1931.

The year by year variation in the percentage distribution of the various types of pneumococci and the combined percentage distribution

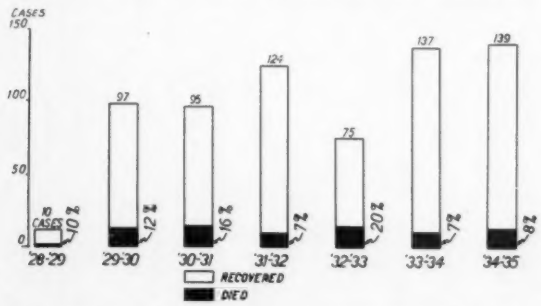

Chart 2.—Summary of 663 cases of pneumococcic pneumonia in children from 1928 to 1935.

for the seven years are shown in tables 1 and 2 for adults and children, respectively. In table 1 it is important to observe that type III pneumonia occurred slightly more frequently in adults than type II pneumonia and that types IV, V, VII and VIII were of almost as great importance from the standpoint of frequency as type II pneumonia. Though type II organisms produced the infection in 8.3 per cent of the cases of pneumonia in adults, they caused pneumonia in only 12 children (table 2).

Charts 3 to 5 for adults and charts 6 and 7 for children show the annual incidence of each type of pneumonia for a seven year period. It will readily be seen that from year to year the occurrence of the individual types of pneumonia varied widely. The marked fall in the total number of cases in 1931-1932 (chart 1) was reflected in the reduction in the total number of cases of type I pneumonia (charts 3 to 7). However, the marked increase in type I pneumonia in 1934-1935 was greater

TABLE 1.—*Pneumococcic Pneumonia in Adults from 1928 to 1936**

Type	1928-1935		1928-1929		1929-1930		1930-1931		1931-1932		1932-1933		1933-1934		1934-1935		1935-1936‡	
	No. of Cases	%	No. of Cases	%	No. of Cases	%	No. of Cases	%	No. of Cases	%	No. of Cases	%	No. of Cases	%	No. of Cases	%	No. of Cases	%
I	725	23.7	108	20.3	98	23.8	99	23.8	71	22.1	92	24.3	116	23.8	141	27.1	127	19.9
II	256	8.4	52	9.8	48	11.6	36	8.7	27	8.4	31	8.2	32	6.6	30	5.8	32	5.0
III	297	9.7	36	6.8	32	7.8	51	12.2	31	9.7	32	8.5	60	12.3	55	10.6	70	10.9
IV	179	5.8	14	2.6	25	6.1	30	7.2	25	7.8	24	6.4	30	6.2	31	6.0	42	6.6
V	230	7.5	37	7.0	28	6.8	44	10.6	15	4.7	23	6.1	25	5.1	58	11.1	53	8.3
VI	51	1.7	5	0.9	7	1.7	1	0.2	10	3.1	10	2.6	13	2.7	5	1.0	8	1.3
VII	194	6.3	24	4.5	34	8.3	35	8.4	26	8.1	17	4.5	31	6.3	27	5.2	85	13.3
VIII	225	7.3	16	3.0	17	4.1	19	4.8	24	7.5	43	11.4	49	10.0	57	10.9	65	10.2
IX	69	2.2	14	2.6	6	1.5	9	2.2	12	3.7	8	2.1	10	2.1	10	1.9	18	2.8
X	17	0.6	1	0.2	7	1.7	1	0.2	0	0.0	4	1.1	3	0.6	1	0.2	3	0.5
XI	18	0.6	3	0.6	2	0.5	0	0.0	5	1.6	4	1.1	0	0.0	4	0.8	3	0.5
XII	32	1.0	5	0.9	3	0.7	5	1.2	2	0.6	2	0.5	12	2.5	3	0.6	14	2.2
XIII	31	1.0	7	1.3	9	2.2	2	0.5	2	0.6	1	0.3	4	0.8	6	1.2	1	0.2
XIV	87	2.8	7	1.3	2	0.5	11	2.7	10	3.1	13	3.4	26	5.3	18	3.5	31	4.8
XVI	17	0.6	1	0.2	2	0.5	1	0.2	0	0.0	5	1.3	1	0.2	7	1.3	6	0.9
XVII	19	0.7	3	0.6	1	0.2	2	0.5	4	1.2	1	0.3	4	0.8	4	0.8	6	0.9
XVIII	63	2.1	4	0.8	9	2.2	9	2.2	5	1.6	9	2.4	15	3.1	12	2.3	14	2.2
XIX	40	1.3	2	0.4	6	1.5	5	1.2	3	0.9	3	0.8	9	1.8	12	2.3	15	2.3
XX	33	1.1	2	0.4	5	1.2	5	1.2	4	1.2	5	1.3	5	1.1	7	1.3	10	1.6
XXI	18	0.6	0	0.0	2	0.5	0	0.0	2	0.6	3	0.8	8	1.6	3	0.6	1	0.2
XXII	20	0.8	0	0.0	0	0.0	2	0.5	5	1.6	4	1.1	7	1.4	2	0.4	6	0.9
Total	2,621		341		343		367		283		334		460		493		610	
	3,066†		532†		411†		415†		321†		378†		488†		521†		639†	

* Types represented by less than 15 cases were omitted.
† Total number of cases, including all cases of pneumococcic pneumonia (Cooper types) and X group and multiple infections.
‡ Statistics for the year 1935-1936 became available after this paper was submitted for publication. There were 639 cases of pneumococcic pneumonia, showing an increase in the total incidence. Noteworthy is the proportional reductions of cases of types I and II and in the increase in the number of cases of types V and VII pneumonia, particularly type VII.

TABLE 2.—*Pneumococcic Pneumonia in Children from 1928 to 1935**

Type	1928-1935		1928-1929		1929-1930		1930-1931		1931-1932		1932-1933		1933-1934		1934-1935	
	No. of Cases	%	No. of Cases	%	No. of Cases	%	No. of Cases	%	No. of Cases	%	No. of Cases	%	No. of Cases	%	No. of Cases	%
I	120	16.0	1	3.5	12	9.5	19	18.8	20	15.2	6	7.6	38	26.8	24	17.2
III	35	4.7	2	6.9	1	0.8	4	4.0	7	5.3	9	11.4	4	2.8	8	5.8
IV	38	5.1	0	0.0	8	6.3	5	5.0	6	4.5	3	3.8	10	7.0	6	4.3
V	40	5.3	2	6.9	9	7.1	3	3.0	10	7.6	4	5.1	5	3.5	7	5.0
VI	80	10.7	1	3.5	9	7.1	8	7.9	14	10.6	12	15.2	18	12.7	18	12.9
VII	18	2.4	0	0.0	3	2.4	6	5.9	3	2.3	2	2.5	4	2.8	0	0.0
VIII	19	2.5	0	0.0	1	0.8	4	4.0	2	1.5	3	3.8	4	2.8	5	3.6
XIV	131	17.5	1	3.5	15	11.8	17	16.8	26	19.7	18	22.8	22	15.5	32	23.0
XIX	39	5.2	0	0.0	8	6.3	5	5.0	9	6.8	4	5.1	6	4.2	7	5.0
Total	520		7		66		71		97		61		111		107	
	749†		29†		127†		101†		132†		79†		142†		139†	

* Types represented by less than 15 cases were omitted.
† Total number of cases, including all cases of pneumococcic pneumonia (Cooper types), X group and multiple infections.

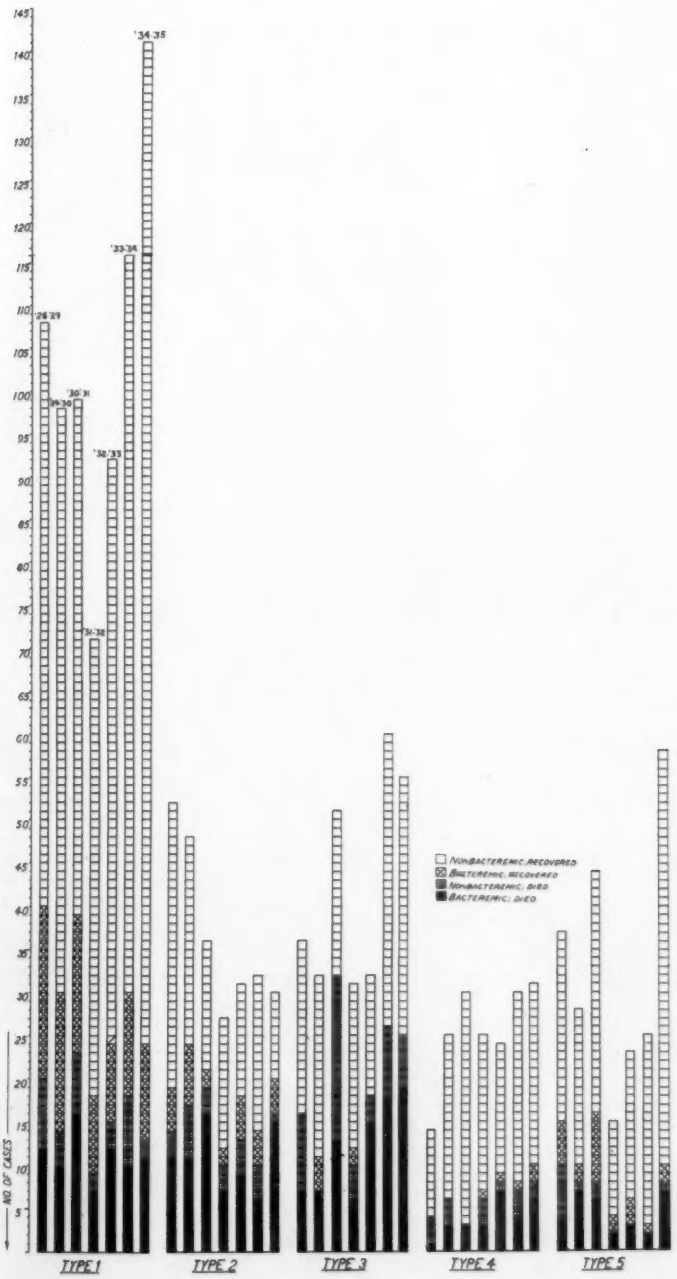

Chart 3.—The yearly variations from 1928 to 1935 in the types of pneumonia in 2,708 adults.

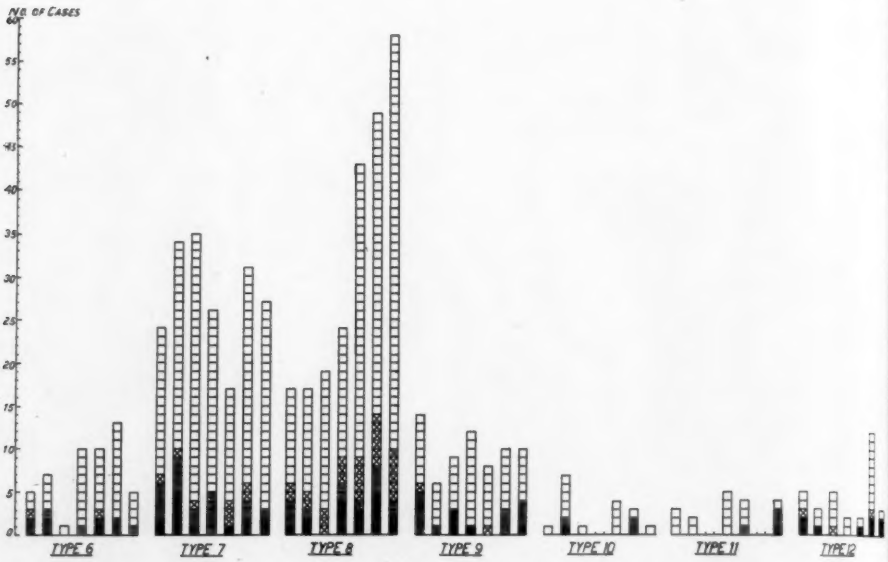

Chart 4.—Chart 3 continued.

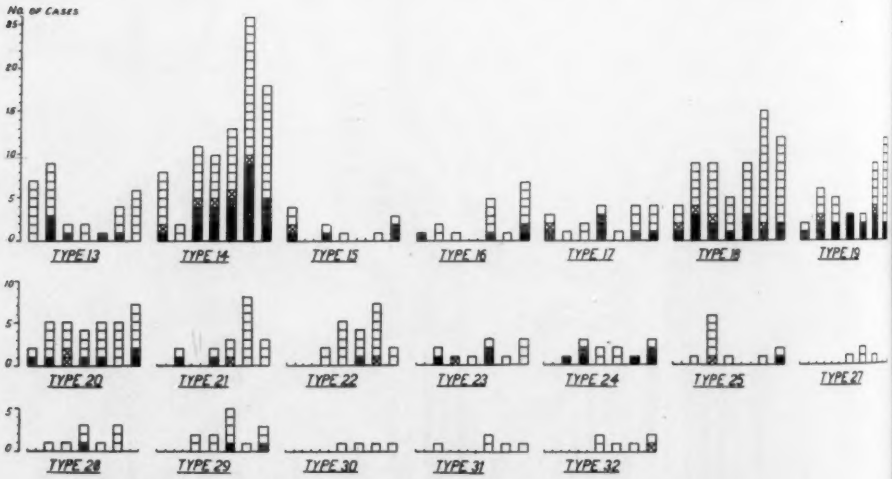

Chart 5.—Charts 3 and 4 continued.

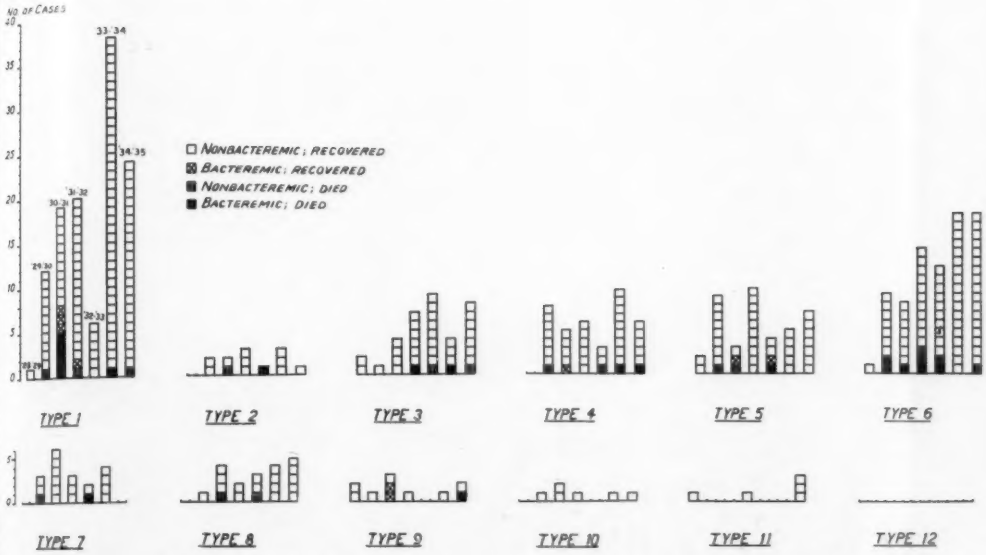

Chart 6.—The yearly variations from 1928 to 1935 in the types of pneumonia in 663 children.

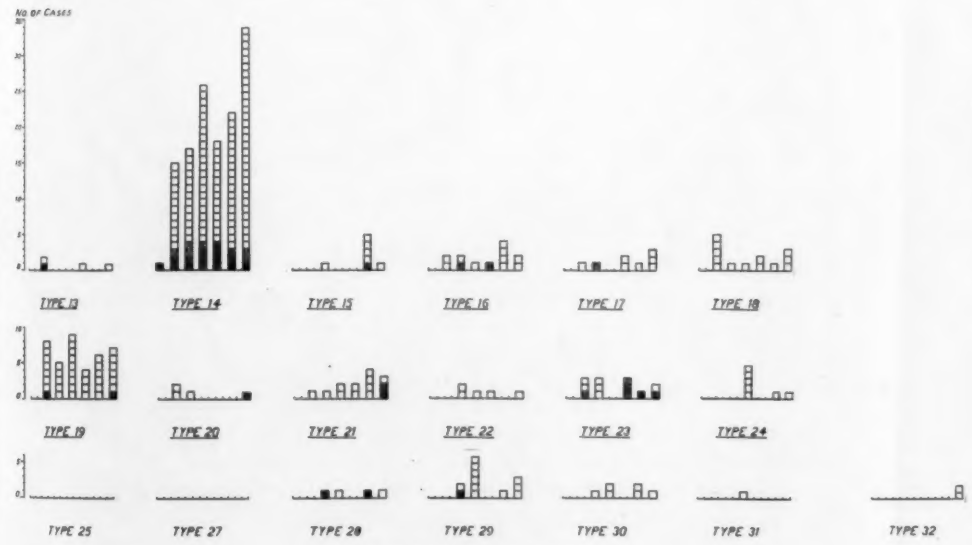

Chart 7.—Chart 6 continued.

than expected, with the prediction based on chart 1. It will be noted that while the number of cases of type I pneumonia increased, the number of cases of type II pneumonia decreased. It must be noted also that type III pneumonia and especially type VIII pneumonia increased in frequency during the last two years. Type V pneumonia, after

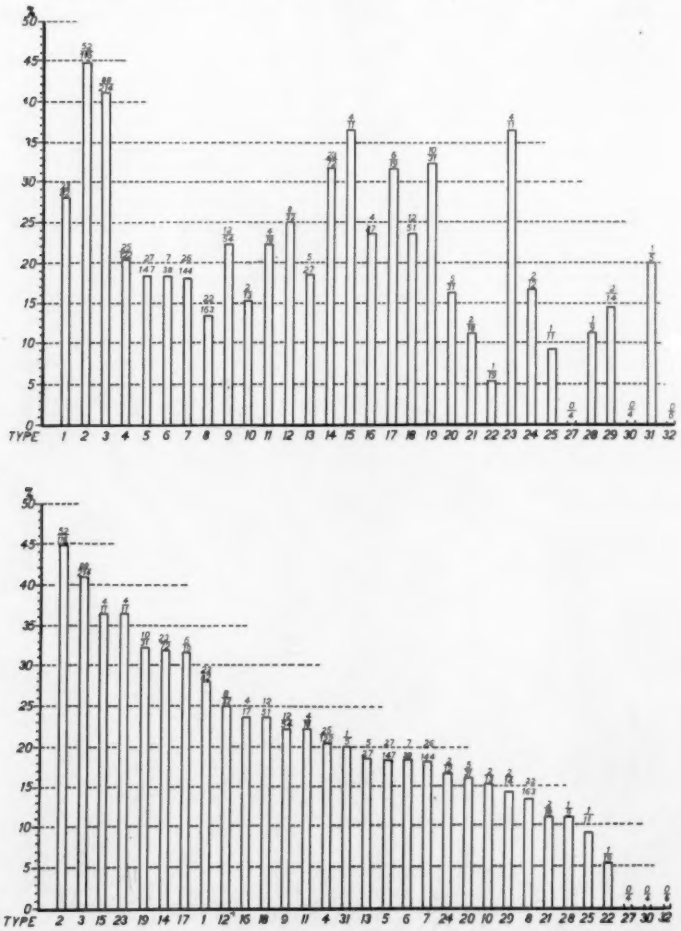

Chart 8.—Mortality percentages in 1,515 cases (in adult patients) of pneumococcic pneumonia from 1928 to 1935 in which no serum was administered. First the types are arranged in numerical order and then according to the mortality percentages.

reaching an apparent maximum in 1931-1932, became infrequent until 1934-1935, when the frequency increased to a new high level. Cases

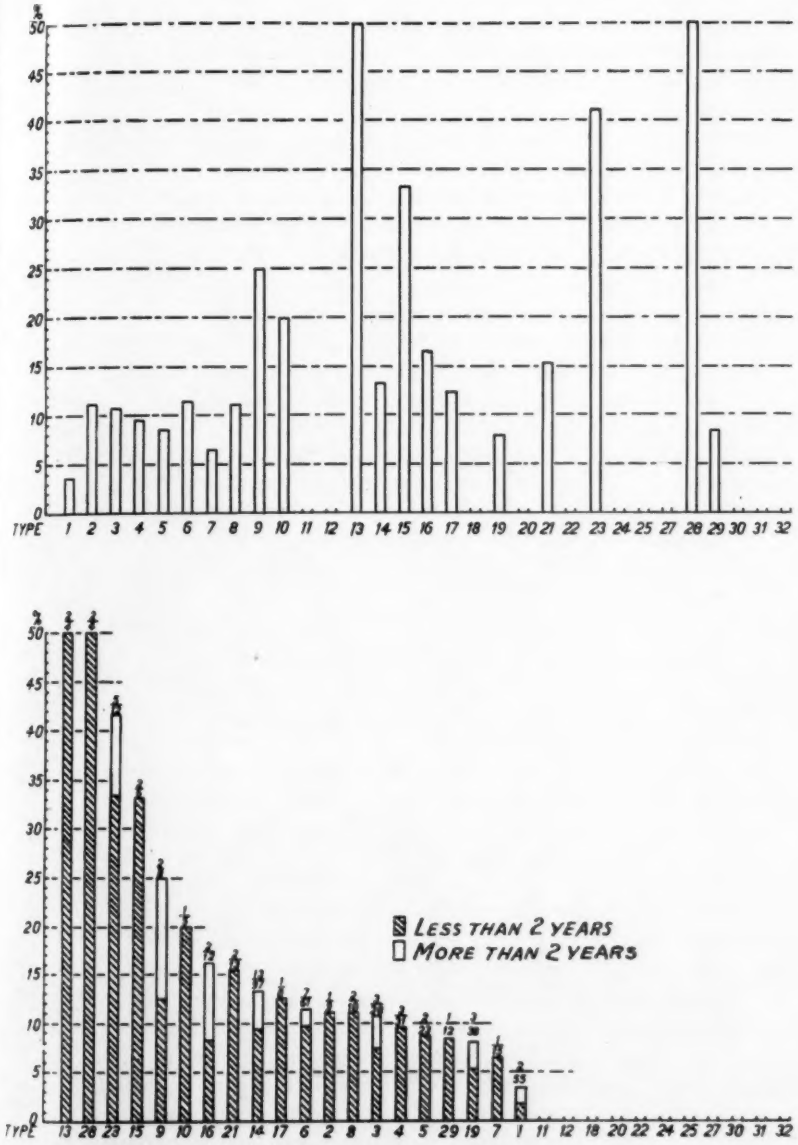

Chart 9.—Mortality percentages in 498 cases (in children) of pneumococcic pneumonia from 1928 to 1935 in which no serum was administered. The lower portion of the chart shows the percentages for 264 children less than 2 years of age and for 234 children more than 2 years of age.

of the other types involved were too few to be considered separately. It may be observed, however, that though in adults the incidence of type III and type VIII pneumonia increased in the later years, this was not true for children.

The annual proportional distribution among the types is given in tables 1 and 2, which show that the various types of pneumococcic pneumonia varied in frequency from year to year. Charts 8 and 9 give information concerning the fatality of the different types, arranged numerically and also in the order of the fatality rate.

The various types of pneumococcic pneumonia varied markedly as to their fatality rates when serum treatment was not given. It is important to note that the cases may be grouped into those in which the mortality rate was more than 25 per cent and those in which it was less than 25 per cent. Some of the types of pneumonia for which serum is available are not among the most fatal types. Chart 9 shows that for only four of the types common to children was the mortality rate over 25 per cent. It may be seen also that eleven types did not cause death among children and that type I, which was eighth in order of frequency of fatality for adults, was least fatal for children. In adults types II, III, XV and XXIII were the most fatal. In children the fatal types were XIII, XXVIII, XXIII and XV. Type XXIII appeared to show a high mortality rate for both children and adults.

In addition to studying the annual variation in the types of endemic pneumococcic pneumonia, a study of the monthly occurrences of nonpneumonic pneumococcic infections of seven important types was undertaken for the year 1934-1935. It was thought that infections of the upper respiratory tract would precede the occurrence of pneumonia, and with this in mind the graph shown in chart 10 was prepared. In no instance did an observed infection of the upper respiratory tract of a given type precede the occurrence of pneumonia due to that type of organism. It is noteworthy that the different types of infection occurred at different times of the year and especially that type VIII infection occurred all through the pneumonia season, while type V was largely encountered during the late spring of the year studied.

There were 449 cases of nonpneumonic pneumococcic infection in adults during the seven year period. The most frequent infections were of types III, VI and VIII, as shown in chart 11. One of the types with a high fatality, type II infection, rarely appeared as a nonpneumonic infection, in spite of the frequency of this type as an incitant of pneumonia. In contrast, type III infection was fatal and frequent in pneumonia and was frequent also in nonpneumonic infections.

An entirely different series of types predominated among the nonpneumonic pneumococcic infections of the respiratory tract in children

(chart 12). Types VI, XIV and XIX were the most important. Next were types XV and XVIII, which are of major importance in causing pneumonia.

Lister and Ordman have recorded that after vaccination of the laborers in certain mines of the Witwatersrand gold fields the types of

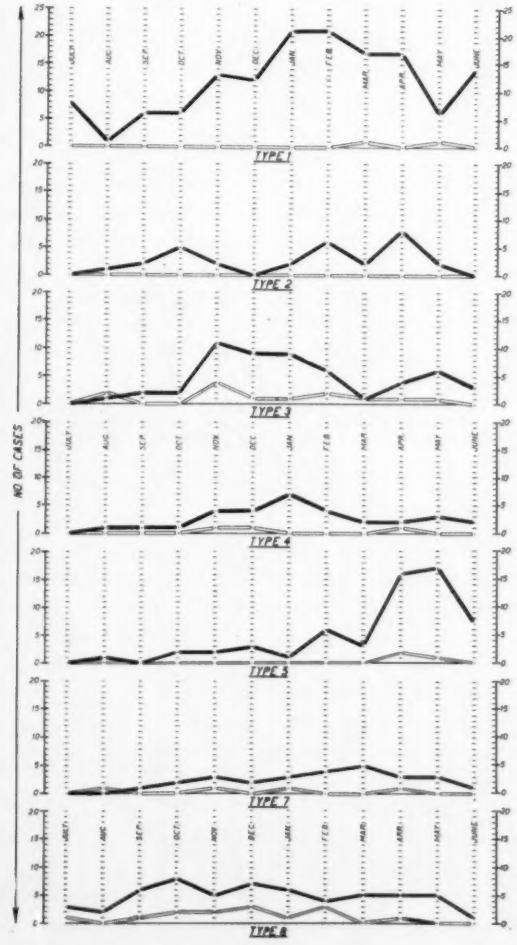

Chart 10.—The monthly incidence in 1934-1935 of pneumonia and nonpneumonic infections of the respiratory tract of the common types. The black lines indicate pneumonic infections and the white lines nonpneumonic infections. Note the sharp rise in type V pneumonic infections in the spring months and that it was not preceded by a rise in the nonpneumonic infections.

pneumococci recovered in cases of pneumonia changed. They found that though the incidence of infections of the respiratory tract was unchanged, the mortality from pneumonia was materially reduced in the mines in which the workers had been vaccinated. The number of cases in which a pneumococcus was not isolated increased by two-thirds (from 11.6 to 31.2 per cent).

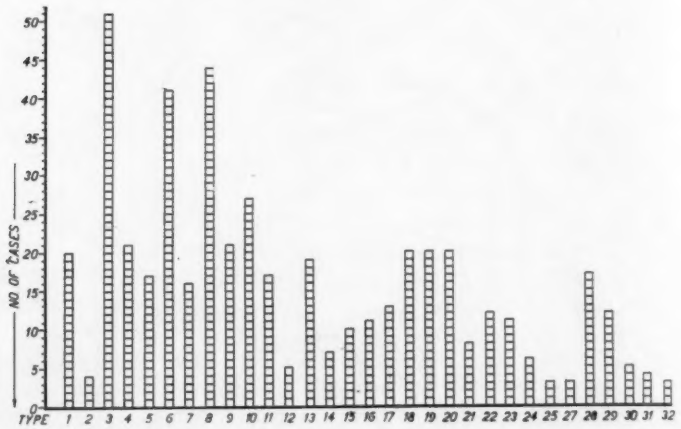

Chart 11.—Types of nonpneumonic pneumococcic infections of the respiratory tract in 473 adults from 1928 to 1935.

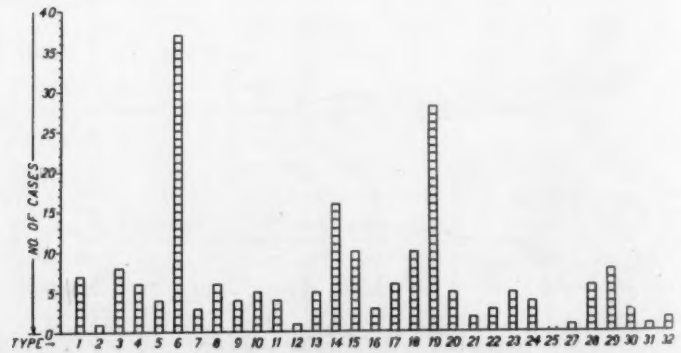

Chart 12.—Types of nonpneumonic pneumococcic infections of the respiratory tract in 204 children from 1928 to 1935.

In the communities where vaccination had not been carried out group B (our type II) pneumonia was the type most frequently found (31.6 per cent), and group C (our type I) was second (18.4 per cent). Group

E (our type III) became relatively more frequent in the communities where vaccination was performed (from 3.9 to 16.9 per cent). The vaccine used on the Witwatersrand was potent for our types I, II and III pneumococci and for a number of others (whether the latter were the same as the Cooper types is at present under investigation). The incidence of group C (our type I) pneumonia was diminished from 18.4 to 11.7 per cent by inoculation. By increasing the strength of the vaccine against group B (our type II) pneumococci, Lister and Ordman said that they were attempting to diminish the number of cases of pneumonia due to that pneumococcus.

CONCLUSIONS AND SUMMARY

The endemic pneumonias are a series of diseases which vary as to their occurrence from year to year and from month to month. They differ in respect to the age of the patients, incidence, mortality, tendency to invade the blood stream and other characters.

Whether the specific types of endemic pneumonia have individual cycles, as suggested by some of the graphs, can be determined only after the results of more studies similar to ours are available and after our own studies have been continued for a longer period. The results may justify immunization against the more fatal or more frequent types, so as to reduce the incidence of these infections. Such studies are required so that physicians and manufacturers may learn what types of pneumonia are prevalent and may require serum for treatment and vaccine for immunization.

There is a marked difference in the types of pneumonia among children and adults living in the same community; it remains for future investigations to determine the reasons for this difference.

PULMONARY CAPACITY IN LOBAR PNEUMONIA

WITH SPECIAL REFERENCE TO COLLAPSE THERAPY

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During the past several years artificial pneumothorax as a therapeutic measure in cases of lobar pneumonia has been enthusiastically employed. Initially pneumothorax was used empirically, and even at the present time the experimental data supporting the rationale of its use are meager (Lieberman and Leopold [1]). The consensus [2] seems to be that the administration of artificial pneumothorax is a useful procedure in the treatment of unilateral lobar pneumonia when it is instituted early in the disease when there are no preexisting adhesions. The effect of this procedure in relieving the distressing symptoms of lobar pneumonia (pleuritic pain, dyspnea and toxic phenomena) has been described by most observers, and many have reported a critical fall in temperature (crisis) in approximately half the cases. The rationale for this procedure has not been subjected to extensive investigation, but the beneficial effects have been attributed to the following factors: (1) relief of pleural pain, (2) compression and immobilization of the acutely inflamed lung, (3) decrease in the absorption of toxins on the affected side due to the shunting of the blood flow from the affected to the unaffected side and (4) mobilization of the antibodies.[3]

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From the Department of Medicine, the School of Medicine and Dentistry, of the University of Rochester, and the Medical Clinic of the Strong Memorial and Rochester Municipal Hospitals.

1. Lieberman, L. M., and Leopold, S. S.: Therapeutic Pneumothorax in Experimental Lobar Pneumonia in Dogs, Am. J. M. Sc. **187**:315, 1934.

2. (*a*) Leopold, S. S., and Lieberman, L. M.: The Present Status of Artificial Pneumothorax in the Treatment of Lobar Pneumonia, Ann. Int. Med. **9**:19, 1935. (*b*) Moorman, L. J.: Artificial Pneumothorax in the Treatment of Pneumonia: Report of Cases, Internat. Clin. **4**:119, 1934. (*c*) Blake, F. G.; Howard, M. E., and Hull, W. S.: Artificial Pneumothorax in the Treatment of Lobar Pneumonia, J. A. M. A. **105**:1489 (Nov. 9) 1935.

3. Perlroth, S., and Topercer, M.: Behandlung der Pneumonien mit künstlichen Pneumothorax, Wien. klin. Wchnschr. **45**:1508, 1932.

The many stimulating reports (see Leopold and Lieberman [2a] and Blake, Howard and Hull [2c] for a review of the literature) on the treatment of lobar pneumonia by pneumothorax have led us to investigate the effects of this procedure on the respiratory function in this disease. The present study concerns the alterations in the vital capacity and other components of the total pulmonary capacity and the roentgenographic measurements during the induction of artificial pneumothorax in cases of typical lobar pneumonia.

METHODS AND MATERIAL

After the necessary preliminary examinations had been made and blood and sputum had been obtained for bacteriologic examination, a diagnostic roentgenogram of the chest was taken. When the patient's condition warranted it, roentgenograms were taken at both maximum inspiration and maximum expiration, according to the technic described by Hurtado and one of us (W. F.).[4] From these roentgenograms the size and expansion of the chest could be followed throughout the course of the disease.

By the time the roentgenographic examinations were completed the prevailing type of organism in the sputum and the group of the pneumococcus had been determined by the *Quellung* method. The diagnosis being confirmed by roentgenograms and the etiologic agent being known, the patient was wheeled in a bed to a quiet room adjoining the laboratory, where measurements of the pulmonary capacity were made and artificial pneumothorax was induced.

Arterial blood was obtained from the radial artery and analyzed for the carbon dioxide and oxygen contents and the oxygen capacity by the method of Van Slyke.[5]

Next the expired air was collected for a two or three minute period in a Douglas bag. The number of respirations was counted. The gas was measured by means of a Sargent wet meter, and the volumes were reduced to standard. We found, as have others,[6] that each patient invariably changes his type of breathing as soon as the mouth-piece is adjusted. The respirations become deeper and less frequent. Consequently, the values for the pulmonary ventilation are valueless and have been discarded. The temperature, pulse rate and respiratory rate charted in the accompanying figures were obtained from the nurses' records.

Measurement of the Pulmonary Capacity.—The midcapacity (the amount of air remaining in the lungs at the end of normal expiration) was determined by the oxygen dilution method without forced breathing, as described by Christie.[7] The length of the rebreathing period was seven minutes in all determinations. Duplicate determinations were usually made. The vital capacity was then mea-

4. Hurtado, A., and Fray, W. W.: Studies of Total Pulmonary Capacity and Its Subdivisions: II. Correlation with Physical and Radiological Measurements, J. Clin. Investigation **12**:807, 1933.

5. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry: II. Methods, Baltimore, Williams & Wilkins Company, 1932.

6. Binger, C. A. L., and Brow, G. R.: Studies on the Respiratory Mechanism in Lobar Pneumonia: A Study of Lung Volume in Relation to the Clinical Course of the Disease, J. Exper. Med. **39**:677, 1924.

7. Christie, R. V.: The Lung Volume and Its Subdivisions: I. Methods of Measurements, J. Clin. Investigation **11**:1099, 1932.

sured graphically by means of a recording spirometer. The reserve and complementary volumes were measured separately. All determinations were made with the patient lying in bed with the head of the bed raised about 45 degrees. Binger and Brow [6] said that such factors as pleuritic pain, anoxemia and general muscular weakness may easily impair the accuracy of measurements of the vital capacity. Fortunately in our experiments the patients who were selected proved to be cooperative, and we believe that the values for this capacity represent the true alterations produced by both the local and the systemic factors caused by acute febrile disease.

With the patient in the same position a needle was inserted in the second interspace in the midclavicular line. After the needle reached the intrapleural space, from 30 to 50 cc. of air was injected, and the intrapleural pressure and the tidal volume were registered simultaneously by means of recording pens. The injection of air was then continued until a maximum of 500 or 600 cc. was reached or until the expiratory pressure was slightly positive.

The patient was then returned to the division for nursing care and rest. Fluids were forced to 4,000 cc., and each patient received at least 10 or 12 Gm. of sodium chloride per diem. In addition to the usual clinical records, the chloride content of the serum and the urinary excretion of chlorides were determined in most cases. Usually from six to eight hours elapsed before the patient was returned to the laboratory, where the aforementioned procedures were repeated, save for the arterial puncture. This process was continued until either the affected lung was collapsed or the crisis appeared. If the patient had preexisting adhesions, air was given until the mean intrapleural pressure equaled the atmospheric pressure.

After the crisis the determinations of the pulmonary capacity were made, and roentgenograms were taken at varying intervals. The examinations of the patients were repeated from one to six months after their discharge from the hospital. After complete recovery a roentgenogram was taken at maximum inspiration for the purpose of estimating the normal capacity.[8]

Owing to the many procedures and the critical condition of the patients, arterial blood and simultaneous records of the intrapleural pressure and the tidal volume were not obtained as frequently as was desired.

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8. The regression formulas for the prediction of the normal capacity are as follows:

1. For males between the ages of 18 and 35
   Vital capacity in liters = roentgenographic volume of chest ($\times$ 0.24) + 1.22.
   Total capacity in liters = $\frac{\text{vital capacity}}{78} \times 100$.
2. For males between ages of 35 and 60
   Total capacity in liters = roentgenographic volume of chest ($\times$ 0.38) —0.17.
   Vital capacity in liters = $\frac{\text{total capacity}}{100} \times 72.8$.
3. For females
   Vital capacity in liters = roentgenographic volume of chest ($\times$ 0.214) + 0.95.
   Total capacity in liters = $\frac{\text{vital capacity}}{71.6} \times 100$.

During the past several years Hurtado and one of us (N. L. K.) have had an opportunity to study two medical students and one patient from the outpatient department who became ill with pulmonary tuberculosis and were treated by artificial pneumothorax. In the case of one (C. J.) the pulmonary capacity was measured both before the onset of the disease and after the establishment of complete pneumothorax (left side). Each of the others was investigated only after collapse of the affected lung. These cases have been included in this study.

Since we are primarily interested in the disturbances in respiratory function during the course of lobar pneumonia and during collapse therapy and not in the therapeutic efficacy, the material was limited to cases of typical early unilateral lobar pneumonia of pneumococcic origin. In one case (T. M.) the pneumonia was of central type without complete lobar consolidation. Nine patients with pneumonia were studied, seven of whom were treated with artificial pneumothorax. There were two cases each of types I, III and XXXII, one each of types II and VII and one of group 4, the type being undetermined. The group included six men and three women, with ages ranging between 18 and 46 years. A brief review of the physiology of respiratory function during the induction of pneumothorax in a relatively healthy subject and during the course of lobar pneumonia is pertinent to an understanding of the alterations in the respiratory bellows during the insufflation of air in a case of pneumonia.

RESULTS

Alterations in the Pulmonary Capacity During the Induction of Pneumothorax in Relatively Healthy Subjects.—Since artificial pneumothorax is usually unilateral, the alterations in the pulmonary capacity are complex. The vital capacity has been studied extensively during the establishment of pneumothorax, but the other components of the total capacity have been neglected. Most investigators[9] have agreed that when a relatively normal lung is collapsed the decrease in vital capacity is not proportional to the amount of air injected. The initial insufflation causes a marked reduction in this capacity, but after several hours there is a slight increase. In subsequent inflations the same

9. (*a*) Anthony, A. J., and Heine: Spirographische Untersuchungen bei Lungenkollaps: I. Mitteilung, Beitr. z. Klin. d. Tuberk. **71**:362, 1929. (*b*) Bendove, R. A.: The Vital Capacity in Artificial Pneumothorax: The Mechanism and the Factors Modifying the Vital Capacity, with Especial Reference to Its Clinical and Prognostic Value in the Collapse Therapy, Arch. Int. Med. **36**:94 (July) 1925. (*c*) Gutman, S.: Capacidad vital, Rev. méd. latino-am. **19**:34, 1933. (*d*) Kochs, K.: Studien über die Vitalkapazität bei künstlichem Pneumothorax, bei Phrenicusexairese und einseitigem Brustheftpflasterverhand, Beitr. z. Klin. d. Tuberk. **73**:734, 1930. (*e*) Myers, J. A., and Bailey, W.: Studies on the Respiratory Organs in Health and Disease: XX. The Value of the Vital Capacity Test in Artificial Pneumothorax Treatment, Am. Rev. Tuberc. **10**:597, 1925. (*f*) Schill, E.: Pneumothoraxstudien: II. Ueber den Zuzammenhang von Vitalcapacität, Pneumothoraxdruck und Lungenkollaps bei mit Pneumothorax behandelten Lungenkranken, Beitr. z. Klin. d. Tuberk. **65**:492, 1927. (*g*) Sieper, H.: Die Vitalkapazität bei der Lungenphthise, besonders bei der Lungencollapstherapie, ibid. **65**:725, 1927.

quantity of air causes various diminutions in the vital capacity in the same subject. The complexity of changes in the vital capacity during the induction of pneumothorax has been variously attributed to the following factors: (1) the amount of air injected, (2) the intrapleural pressure (type of pneumothorax), (3) the structural and functional status of the affected lung, (4) status of the contralateral lung, (5) the stability of the mediastinum, (6) movements of the diaphragms and (7) the elasticity of the thoracic cage. An interplay of these factors can cause a multiplicity of alterations in the vital capacity and the other components of the total pulmonary capacity.

Obviously, alterations in the vital capacity cannot be interpreted without a knowledge of the volume of residual air. Because of the difficulties in measuring this volume, it has received little attention.[10] Anthony and Heine [11] found that after unilateral pneumothorax the amount of residual air was diminished but that the diminution varied markedly. Furthermore, the variation was dependent not on the volume of the pneumothorax but on the rigidity of the mediastinum, alterations in the movements of the thoracic cage, the anatomic changes in the collapsed lung and a theoretical capacity designated by them as the "vital minimal volume." The normal capacity (midcapacity) was diminished, but the reduction was smaller than the volume of the pneumothorax. These investigators observed also that both the volume of the pneumothorax and that of the contralateral lung increased after the insufflation of air but that the increase of the latter was not so great as the increase of the volume of the pneumothorax.

The alterations in the pulmonary capacity following unilateral pneumothorax are shown in figure 1. In the first case (C. J.), in which there was complete pneumothorax of several months' duration on the left side, the total and vital capacities and the midcapacity were moderately reduced, being 68, 57 and 68 per cent, respectively, of the predicted capacity. The amount of residual air was actually higher than the predicted value and only slightly less than that found before the establishment of pneumothorax.

In the second patient (J. K.) the right lung was collapsed about 70 per cent. The measurement of the pulmonary capacity was made three hours after a refill was given. The intrapleural pressure at that time was —4 cm. of water at the end of normal inspiration and atmospheric (0 cm. of water) at the end of expiration. Here again,

10. Wolf, H. J.: Die nervöse Atmungsregulation bei der Lungentuberkulose: III. Der Einfluss des künstlichen Pneumothorax auf den Ausfall der Funktionsprüfung der Atmung und auf das Verhalten der Lungenvolumina, Ztschr. f. d. ges. exper. Med. **63**:616, 1928.

11. Anthony, A. J., and Heine: Spirographische Untersuchungen bei Lungenkollaps: II and III. Mitteilung, Beitr. z. Klin. d. Tuberk. **73**:51, 1929; footnote 9a.

the total and vital capacities and the midcapacity all were proportionally reduced, approximately 40 per cent, while the amount of residual air was 56 per cent of that predicted.

The results in the third case (D. F.) were similar to those in the first. The determination of the pulmonary capacity was made several days after the last refill was given, at which time the intrapleural pressure was —4 cm. of water at normal inspiration and 0 cm. of water at expiration. The left lung was collapsed about 80 per cent. There was a reduction of from 50 to 55 per cent in the total and vital capacities and the midcapacity, while the amount of residual air was 65 per cent of that calculated.

In these cases all the values for the ratio $\frac{\text{residual air}}{\text{total capacity}} \times 100$ were slightly increased, owing to a greater reduction in the vital capacity than in the volume of residual air. Likewise, the values for the ratio $\frac{\text{midcapacity}}{\text{total capacity}} \times 100$ were slightly elevated. There was no disturbance,

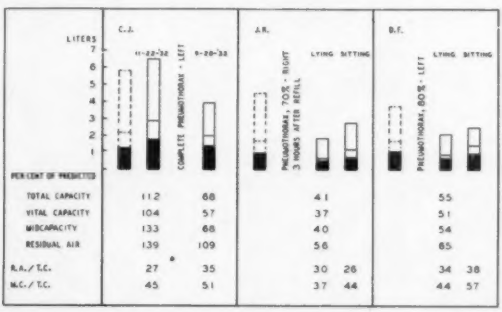

Fig. 1.—Predicted and observed pulmonary capacities in patients with unilateral pneumothorax. The columns with broken lines represent the predicted values, while the ones with solid lines represent the observed pulmonary capacity. In this and subsequent figures the black area represents the residual air and the white space above represents the vital capacity. The line dividing the vital capacity is the level of the midcapacity.

however, in the components of the vital capacity, the complementary air comprising approximately 80 per cent of the vital capacity.

Anthony and Heine [11] found that the alterations in the vital capacity due to a change in posture in persons with pneumothorax were similar to but not as marked as the changes in normal subjects. The effect of posture was studied in two of our patients (fig. 1). When the subject assumed a sitting position there was a marked increase in the total and vital capacities and the midcapacity and in the amount of reserve air. There was a moderate increase in the amount of residual

Roentgenographic Measurements

Patient	Lung Affected	Number of Days After Onset	Stage of Disease	Amount of Air, Cc.	Diaphragm at Maximum Inspiration				Area of Pulmonary Fields, Maximum Inspiration, Sq. Cm.	Area at Maximum Expiration / Area at Maximum Inspiration × 100, %	Movement of Rib, Degrees	Cardiac Measurements	
					Right		Left					Area, Sq. Cm.	Transverse Diameter, Cm.
					Height, Cm.	Excursion, Cm.	Height, Cm.	Excursion, Cm.					
Pneumothorax in Early Pulmonary Tuberculosis													
C. J.	Left, complete collapse....	...	Before collapse.....	...	23.1	4.6	25.1	3.8	652	69.3	21	...	....
			After collapse.....	...	25.3	7.7	25.6	0.4	630	73.9	Right 22 Left 7	...	....
J. K.	Right, 70% collapse.....	...	After collapse.....	...	15.8	—2.7	23.2	4.7	518	80.5	..	...	....
D. F.	Left, complete collapse....	...	After collapse.....	...	18.6	2.3	21.2	1.0	443	77.6	..	...	....
Lobar Pneumonia													
W. A.	Right.....	...	Consolidation.....	...	21.8	0.6	24.9	3.9	574	73.2	Right 0 Left 21	146	13.1
			Partial resolution.....	...	20.6	...	24.7	...	527	....	..	137	13.6
			Complete recovery.....	...	22.7	5.4	25.6	5.5	580	62.1	Right 21 Left 20	124	12.8
E. G.	Right.....	...	Consolidation.....	...	22.4	...	26.0	...	670	....	..	180	15.9
			Spread.....	...	23.0	...	25.6	...	680	....	..	185	15.7
			Complete resolution.....	...	23.8	5.7	26.7	7.2	696	65.9	19	168	15.6
			Complete resolution.....	...	25.6	6.0	27.8	7.1	745	64.3	16	...	....
Lobar Pneumonia Treated by Collapse Therapy													
A. D.	Right.....	3	Consolidation.....	...	....	...	....	...	...	....	..	140	13.1
		4	.....	500	25.2	...	25.8	...	651	....	..	136	13.1
		6	Spread of pleural pain.....	500	23.3	..	23.1	...	580	....	..	136	12.9
		12	Clearing.....	...	25.8	...	26.0	...	680	....	..	123	11.9
		37	Recovery.....	...	23.7	4.6	25.7	4.9	663	64.7	22	102	11.1

E. L.	Right	3	Consolidation	...	19.0	...	22.5	...	431	....	..	123	12.4
		3	.....	700	18.3	...	22.8	...	462	....	..	...	....
		4	.....	450	18.9	...	22.1	...	480	....	..	124	12.8
		4	.....	350	19.4	...	23.4	...	502	....	..	...	....
		6	.....	...	....	...	....	...	...	....	..	127	13.2
		9	.....	...	22.3	...	21.1	...	514	....	..	105	11.8
		19	Resolution	...	22.6	...	23.1	...	539	....	..	107	12.6
		48	Recovery	...	20.5	4.4	21.9	3.9	487	65.3	22	114	9.7
		111	Recovery	...	20.0	4.6	21.0	3.2	460	68.0	23	...	....
C. M.	Left	3	Central consolidation	...	....	...	....	...	...	....	..	105	11.3
		4	Spread	...	23.3	3.9	24.6	4.2	648	68.7	Right 20 Left 15	122	12.5
		5	.....	650	21.3	...	23.3	...	575	....	..	127	13.3
		6	.....	650	19.5	...	21.6	...	535	...	..	...	....
		11	Partial resolution	...	22.3	...	22.6	...	600	....	..	126	13.3
		49	Recovery	...	23.7	4.4	25.0	4.2	650	66.8	20	110	11.9
		58	Recovery										
T. M.	Right	2	Consolidation	...	20.7	...	22.6	...	510	....	..	98	11.8
		3	.....	500	22.1	..	24.2	...	610	....	..	...	....
		4	.....	300	22.3	...	21.8	...	587	....	..	140	14.2
		46	Recovery	...	20.1	4.9	22.0	4.9	539	63.8	20	123	13.8
I. G.	Left	3	Pleural pain	...	18.0	0.8	18.2	1.9	410	90.2	..	112	12.1
		15	.....	350									
		101	Recovery	...	16.6	2.2	18.0	2.0	413	77.5	13	99	11.8
M. L.	Right	2	Pleural pain	...	17.4	...	22.4	...	445	....	..	...	....
		3	.....	500	16.6	...	22.1	...	439	....	..	...	....
		3	.....	500	17.5	...	22.4	...	455	....	..	...	....
		4	.....	500	19.5	...	24.2	...	510	....	..	...	....
		5	.....	550	19.4	...	24.1	...	510	....	..	...	....
		48	Recovery	...	17.8	4.3	22.3	6.2	482	63.3	22	...	....
		111	Recovery	...	17.7	3.8	21.3	4.8	468	65.8	25	...	....
W. H.	Right	2	Consolidation	...	22.0	3.8	26.4	2.9	512	80.5	8	...	....
		3	.....	500	23.0	...	25.3	...	551	....	..	...	....

air, while the change in the amount of complementary air varied. The percentage of change was similar to that found in normal persons.[12]

The size of the chest (the area of the pulmonary fields) in one case (C. J.) was essentially the same after the injection of air as before, but in all cases the ability to expand the thorax was markedly diminished (table). The excursions of the diaphragm and the rotation of the ribs were greatly reduced on the affected side, while on the opposite side they were actually increased.

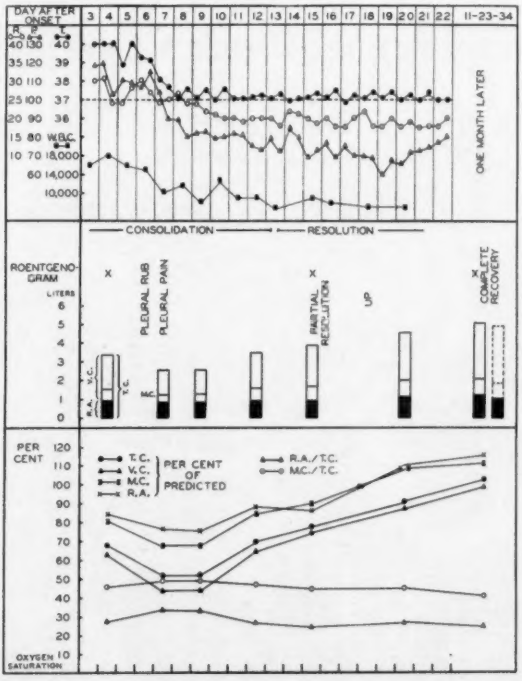

Fig. 2.—Predicted and observed pulmonary capacities during the course of lobar pneumonia. In this and subsequent charts the symbols (in the lower division) for the various absolute and relative values of the pulmonary capacity are identical. The column with broken lines at the extreme right represents the predicted values for the pulmonary capacity. At the left are recorded the respiratory and pulse rates, the temperature in degrees centigrade and the leukocyte count. This patient, W. A., a man aged 22, was admitted to the hospital on Oct. 7, 1934, and was discharged on October 26. In this case and in all the other cases in this series culture of the blood was sterile. The lower lobe of the right lung was the site of pneumonia due to type VII pneumococci.

12. Hurtado, A., and Fray, W. W.: Studies of Total Pulmonary Capacity and Its Subdivisions: III. Changes with Body Posture, J. Clin. Investigation **12**:825, 1933.

Alterations in the Pulmonary Capacity During the Course of Lobar Pneumonia.—According to the observations of Myers [13] and Arnett,[14] soon after the onset of lobar pneumonia the vital capacity is reduced tremendously. The maximum reduction is reached near the day of the crisis, and the increase in this capacity is the first evidence of resolution. Eventually there is a return of the vital capacity to the prepneumonic level, unless pleural adhesions are present to prevent it. Furthermore, there is no parallelism between the extent of the pulmonary lesion and the reduction in the vital capacity (Myers [13] and

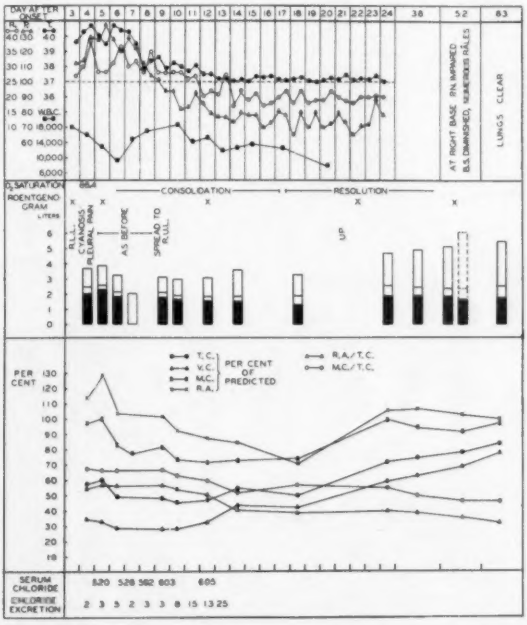

Fig. 3.—Observed pulmonary capacity during the course of lobar pneumonia. The serum chloride content is expressed in milligrams per hundred cubic centimeters and the amount of sodium chloride excreted per diem in grams. The blood for these determinations was collected under oil without stasis by the resident physicians of the hospital, and the analyses were made by technicians in the clinical laboratory. This patient, E. G., a man aged 42, was admitted to the hospital on March 18, 1935, and was discharged on April 8. The upper and lower lobes of the right lung were the site of pneumonia due to type II pneumococci.

13. Myers, J. A.: The Vital Capacity of the Lungs, Baltimore, Williams & Wilkins Company, 1925.

14. Arnett, J. H.: Vital Capacity of the Lungs: Changes Occurring in Health and Disease, J. Clin. Investigation **14**:543, 1935.

Anthony [15]). Binger and Brow [6] found that a "constant relationship existed between the persistence and disappearance of symptoms and fluctuations of the functional residual air. This capacity was diminished during the persistence of pathological signs in the lungs, and returned to normal as the pathological signs disappeared." Measurements of the volume of residual air during lobar pneumonia have been made in only a few cases.[15] Usually it is reduced but not in proportion to the pulmonary involvement. The degree of diminution in the volume is influenced by a number of factors, which will be discussed later.

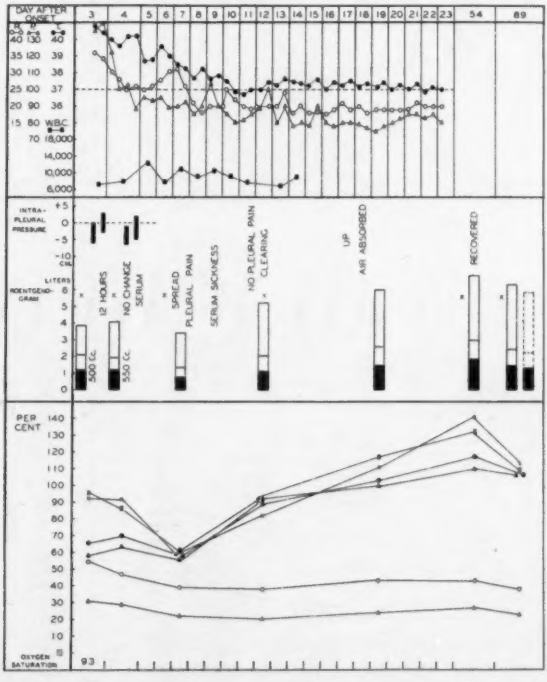

Fig. 4.—This patient, A. D., a man aged 21, was admitted to the hospital on Oct. 15, 1934, and was discharged on November 4. The lower lobe of the right lung was the site of pneumonia due to type I pneumococci.

The values for the total pulmonary capacity and its subdivisions during the course of lobar pneumonia are presented in figures 2 and 3. Observations in seven cases prior to the insufflation of air in the pleural

15. Anthony, A. J.: Untersuchungen über Lungenvolumina und Lungenventilation, Deutsches Arch. f. klin. Med. **167**:129, 1930.

cavity are shown in figures 4 to 10. Early in the course of the disease (from the second to the fourth day after the onset) the vital capacity was markedly reduced (from 35 to 65 per cent of the predicted values) in all cases. There appeared to be no general relationship between the extent of the pulmonary involvement and the reduction in this capacity. However, several patients (E. G., E. L., I. G. and M. L.) who complained of pleuritic pain showed a greater reduction in this capacity than those who did not complain of this type of pain. Interestingly, in one patient (W. A.) pleural pain developed on the seventh day of the disease, and the vital capacity fell from 63 to 44 per cent of the predicted value.

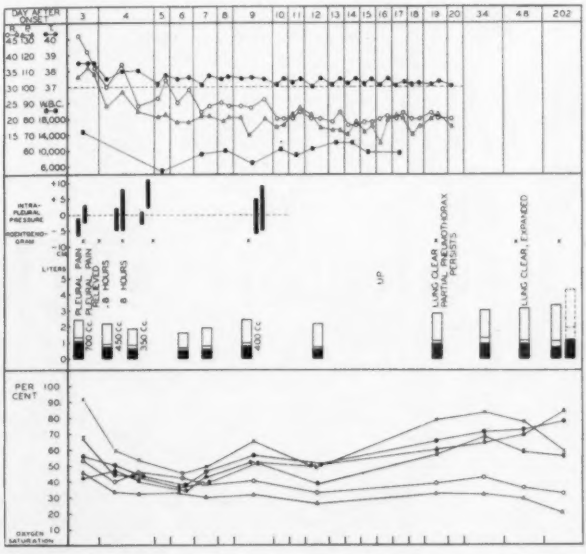

Fig. 5.—This patient, E. L., a woman aged 45, was admitted to the hospital on Oct. 27, 1934, and was discharged on November 13. The middle and lower lobes of the right lung were the site of pneumonia due to type IV pneumococci.

The alterations in the residual air during the early stages of lobar pneumonia were variable. There was a slight reduction (from 68 to 92 per cent) of this capacity in three patients (W. A., A. D. and T. M.), while in the remainder the amount of residual air was actually increased. Similar observations were found with regard to the midcapacity, except that the reduction was more marked. The greater diminution in the midcapacity than in the amount of residual air may

have been due to changes in the volume of reserve air, but it was found that the latter volume constituted a normal percentage of the vital capacity.

There was a reduction in the total capacity (from 55 to 80 per cent), but not so marked as that in the vital capacity, owing to the relative increase in the amount of residual air. Pleural pain likewise influenced the diminution in this capacity.

The relative values are of great interest in these cases. Because of the relatively greater reduction in the vital capacity than in the amount

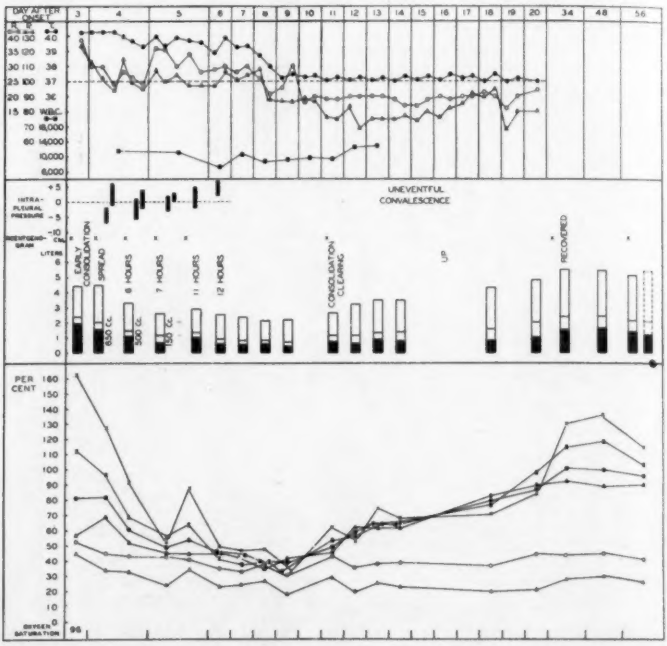

Fig. 6.—This patient, C. M., a man aged 18, was admitted to the hospital on Dec. 11, 1934, and was discharged on December 28. The upper lobe of the left lung was the site of pneumonia due to type III pneumococci.

of residual air, the ratio $\frac{\text{residual air}}{\text{total capacity}} \times 100$ was increased in all patients except one (T. M.). This patient had a central type of pneumonia. A similar but less marked change was found in respect to the ratio $\frac{\text{midcapacity}}{\text{total capacity}} \times 100$.

The measurements of the pulmonary capacity were followed throughout the course of the disease in two cases (figs. 2 and 3). As

the disease progressed all the absolute values were further decreased. This continued until the crisis, when they remained stationary for several days and then gradually returned to the predicted values within a period of one or two months after the onset of the disease. The return was gradual and never complete in one case (E. G.), owing probably to thickening of the pleura at the base of the right lung. A spread of the consolidation to another lobe (E. G.) further reduced the absolute values for all the components.

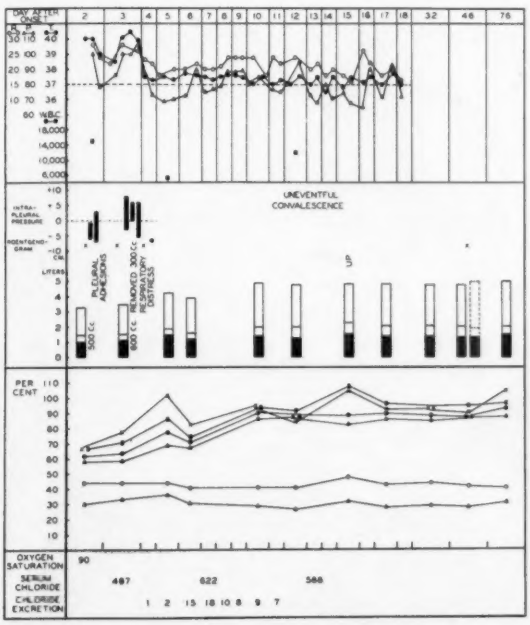

Fig. 7.—This patient, T. M., a man aged 45, was admitted to the hospital on Dec. 18, 1934, and was discharged on Jan. 3, 1935. The upper lobe of the right lung was the site of pneumonia due to type III pneumococci. There was pulmonary fibrosis throughout both pulmonary fields.

Details of the roentgenographic measurements are charted in the accompanying table. During the stage of consolidation there was a marked reduction in the patient's ability to expand the chest, as evidenced by alterations in the values for the excursions of the diaphragm, movement of the ribs and the ratio $\frac{\text{area at maximum expiration}}{\text{area at maximum inspiration}} \times 100$. Similar alterations in the movement of the ribs and diaphragm have been

observed by Jung and Van Allen.[16] The level of the diaphragm at maximum inspiration was generally higher on the involved than on the contralateral side. As the process in the lung resolved the height of the pulmonary field increased. Since the two sides of the thorax cannot act absolutely independently, these changes were reflected to a lesser degree on the opposite side. The area of the pulmonary fields (including the cardiac area) increased somewhat as the patient convalesced. Both the area and the transverse diameter of the heart were

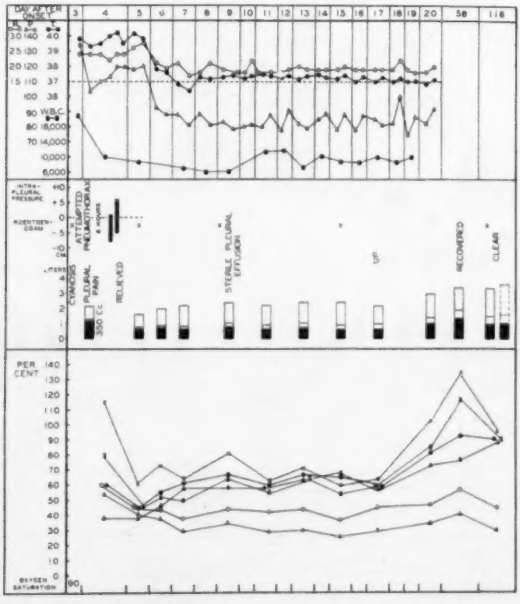
DAY AFTER ONSET
3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 58 116
PLEURAL PAIN
RELIEVED
STERILE PLEURAL EFFUSION
RECOVERED
CLEAR
PER CENT

Fig. 8.—This patient, I. G., a woman aged 29, was admitted to the hospital on Jan. 4, 1935, and was discharged on January 21. The lower lobe of the left lung was the site of pneumonia due to pneumococci of group 4, type XXXII.

increased during the height of the disease and then gradually became smaller as the process abated. Levy[17] observed similar changes in the cardiac shadow.

16. Jung, T., and Van Allen, C.: A Method of Recording Respiratory Movements on a Single Roentgenogram, Nat. M. J. China **17**:195, 1931.

17. Levy, R. L.: The Size of the Heart in Pneumonia: A Teleroentgenographic Study, with Observations on the Effect of Digitalis Therapy, Arch. Int. Med. **32**:359 (Sept.) 1923.

The changes in the arterial blood were typical of lobar pneumonia (Stadie,[18] Barach and Woodwell,[19] Meakins and Davies [20] and others). The oxygen saturation was below normal in all but one patient (C. M.). The oxygen capacity was normal. There was a moderate reduction in the carbon dioxide content of the arterial blood (a range of from 35 to 44 volumes per cent). When the value for the ratio $\frac{\text{residual air}}{\text{total capacity}} \times 100$ was more than 45 per cent, a certain degree of anoxemia was always present.

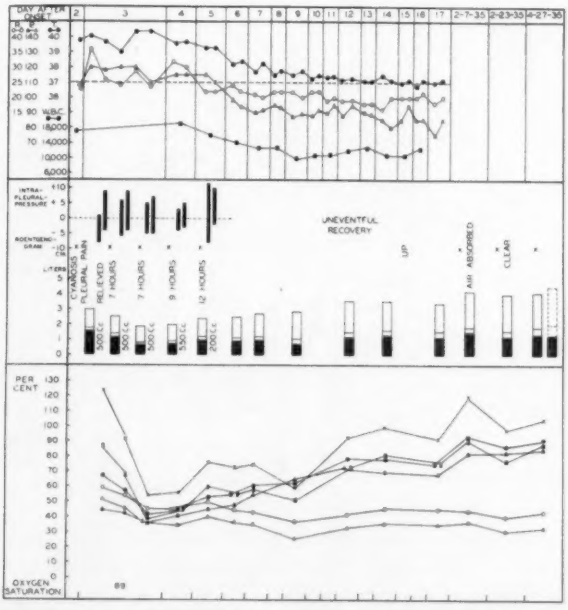

Fig. 9.—This patient, M. L., a woman aged 46, was admitted to the hospital on Jan. 8, 1935, and was discharged on January 24. The lower lobe of the right lung was the site of pneumonia due to pneumococci of group 4, type XXXII.

Determinations of the Pulmonary Capacity of Patients with Lobar Pneumonia Treated by Collapse Therapy (Clinical Observations).—Most observers [2] have agreed that artificial pneumothorax in lobar

18. Stadie, W. C.: The Oxygen of the Arterial and Venous Blood in Pneumonia and Its Relation to Cyanosis, J. Exper. Med. **30**:215, 1919.

19. Barach, A. L., and Woodwell, M. N.: Studies in Oxygen Therapy: II. In Pneumonia and Its Complications, Arch. Int. Med. **28**:394 (Oct.) 1921.

20. Meakins, J. C., and Davies, H. W.: Respiratory Function in Disease, London, Oliver & Boyd, 1925.

pneumonia is effective only when treatment is instituted early and when the affected lung is quickly and completely compressed. All of our patients were treated early in the course of the disease (on or before the fourth day), but complete collapse or nearly complete collapse was effected in only two (E. L. and M. L.) and moderate collapse in one (C. M.). Total collapse in the other cases was not obtained for several reasons: (1) pleural adhesions were present (T. M.), (2) either the quantity of air injected was too small or the air was not injected fast enough (A. D. and I. G.) or (3) the process spread to the contralateral lung (W. H.). Usually at each treatment sufficient air was given to establish a positive expiratory pressure with a mean

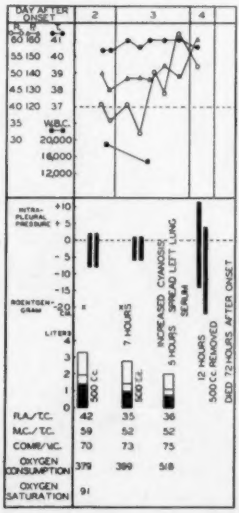

Fig. 10.—This patient, W. H., a man aged 21, was admitted to the hospital on March 11, 1935, and died on March 13. The upper lobe of the right lung was the site of pneumonia due to type I pneumococci.

intrapleural pressure in the neighborhood of 0 mm. of water or slightly positive. The total amount of air injected ranged from 350 cc. (I. G.) to 2,250 cc. (M. L.). The clinical results were not striking. Pleural pain when present was relieved in all cases (E. L., I. G. and M. L.). Two patients (E. L. and I. G.) volunteered the remark that they "felt better after the air" was given. The injection of air caused no noticeable change in the pulse or respiratory rates except in one case (T. M.), in which respiratory distress developed during the second treatment. After 300 cc. was removed the distress was relieved. Obvi-

ously, because of the small series of cases, one is not justified in drawing any conclusions concerning the production of a crisis by artificial pneumothorax. Only two complications were encountered, a sterile pleural effusion (I. G.) and acute respiratory distress (T. M.). One of the seven patients (W. H.) treated by collapse therapy died (seventy-two hours after the onset of the disease). At the time treatment was instituted the patient showed physical and roentgenographic evidence of consolidation of the upper lobe of the right lung. Twenty-four hours before death occurred a roentgenogram showed that the left lung was clear. Clinically there was a rapid spread to the opposite side after this, and at autopsy there was early involvement of the entire left lung.

Details of the alterations in the pulmonary capacity are given in figures 4 to 10. After the first injection of air the absolute values for all the components were rapidly and proportionally reduced, and subsequent insufflations caused a less marked diminution. The various capacities expressed in percentages of the predicted values were almost identical after several injections. However, the reduction in the amount of residual air was slightly less than that of the other volumes. There appeared to be some relation between the amount of air given and the degree of diminution in the various capacities. As a rule the decrement of the capacities amounted to a little more than 50 per cent of the predicted values (from 40 to 50 per cent in E. L., C. M., I. G. and M. L. and from 50 to 60 per cent in A. D.). In one case (T. M.) the injection of 800 cc. of air over a period of twenty-four hours caused no reduction in the volumes.

Interestingly enough, during the establishment of pneumothorax the ratios $\frac{\text{residual air}}{\text{total capacity}} \times 100$ and $\frac{\text{midcapacity}}{\text{total capacity}} \times 100$ were decreased in all cases but one (T. M.), indicating a more normal relationship of the volume of residual air, the midcapacity and the vital and total capacities.

After the crisis the values for all the different capacities gradually returned to normal. However, the restoration was more rapid in patients without pneumothorax (W. A. and E. G.) than in those treated by this procedure. In two patients (E. L. and M. L.) the vital and total capacities did not reach their predicted values, even four or six months after the onset of the disease. This discrepancy was due to the formula applied for the prediction. The formula used in these calculations was based on the values obtained for normal women between the ages of 18 and 30 years. Measurements recently made in this clinic for normal women in older age groups indicate that this formula does not apply to older women.

ROENTGENOGRAPHIC MEASUREMENTS

Results of the various measurements are presented in the accompanying table. The height of the pulmonary field on the affected side

and the area of the pulmonary field were larger during maximum collapse than before the establishment or after the disappearance of the pneumothorax (see cases E. L. and M. L., in which the affected lung was almost completely compressed). The measurements in the other cases showed no consistent changes. Establishment of pneumothorax in patients with lobar pneumonia had no effect on the degree of dilatation of the heart.

COMMENT

Pulmonary Capacity in Patients with Unilateral Pneumothorax.—The total and vital capacities and the midcapacity are proportionally reduced in patients with unilateral pneumothorax of several months' duration. It has been shown that the decrease in residual air is not proportional to that of the other capacities, resulting in a high value for the ratio $\frac{\text{residual air}}{\text{total capacity}} \times 100$. If the determinations are made shortly after a refill is given, the diminution in this capacity is more marked (J. K.) than when it is measured several days later (C. J. and D. F.). Furthermore, our results show that for pneumothoraces of similar volumes the reduction in the amount of residual air was greater when the affected lung was rapidly collapsed (E. L. and M. L.) than when it was more slowly compressed (C. J. and D. F.). In other words, some time after the injection of air there occurs a gradual increase in the volume of the residual air. This increment is probably due to an increase in the volume of the contralateral lung, usually referred to as "compensatory emphysema." Anthony and Heine [9a,11] observed that the volume of the contralateral lung increases after the establishment of unilateral pneumothorax.

The pathogenesis of this type of emphysema is somewhat different from that of the obstructive type. The conditions (such as pneumonia, congestive heart failure, anoxemia, pulmonary fibrosis and pulmonary atelectasis) in which "compensatory emphysema" appears are not usually associated with bronchial obstruction. Prinzmetal [21] said that he believed this is due to pulmonary distention. He has shown in acute experiments on animals that in conditions in which there are an increased carbon dioxide and a decreased oxygen tension in the inspired air the intrapleural pressure is more negative and the size of the chest increases. When he exposed animals to low oxygen tension over a period of weeks, he found that the alveoli of the lungs were greatly dilated. Other investigators found similar changes but with the additional findings of marked congestion of the capillaries (Hurtado [22]

21. Prinzmetal, M.: The Relation of Inspiratory Distention of the Lungs to Emphysema, J. Allergy **5**:493, 1934.

22. Hurtado, A.: Respiratory Adaptation of the Indian Natives of the Peruvian Andes: Studies at High Altitudes, Am. J. Anthrop. **17**:137, 1932.

and Hurtado and others [23]) and a decrease in the distensibility of the lungs (Christie and Meakins [24]). In many of these conditions, especially congestive heart failure and compression of one lung, in which "compensatory emphysema" develops the circulatory rather than the respiratory factors play the major rôle. Von Basch [25] on the basis of physical experiments and Christie and Meakins [24] on the basis of in vivo observations have shown that the compensatory emphysema associated with cardiac disease is due to circulatory adjustments. More recently McIntosh [26] pointed out that after thoracoplasty there is increased congestion of the contralateral lung, accompanied with an increase in the volume of the residual air. Although the mechanism involved in the production of this type of emphysema has not been determined, we believe, from the information available, that the important etiologic factor is circulatory rather than respiratory. However, if either of these mechanisms continues for any considerable period, a loss of pulmonary elasticity, emphysema and a decreased negative intrapleural pressure result. If this process is initiated by the respiratory mechanism, one may expect to find a stimulus for increased inspiratory muscular activity, leading to pulmonary distention and hyperventilation of the whole lung or portions of it. A little later, or even in the absence of pulmonary distention, there occurs congestion of the capillaries, with decreased distensibility of the lungs, accompanied with a less negative intrapleural pressure. The engorgement of the alveolar capillaries and the increased rigidity of the lungs will increase the number and size of the alveolar air spaces, thus tending to increase the amount of residual air and decrease the vital capacity.

The relative increase in the amount of residual air in unilateral pneumothorax of some months' duration is in all probability due to such a process. It has been generally agreed by most recent investigators (Coryllos and Birnbaum [27] gave a review of the literature) that the circulation in the collapsed lung is progressively impaired. Since the output of the heart remains unaltered or slightly decreased in some

23. Hurtado, A.; Kaltreider, N. L., and McCann, W. S.: Respiratory Adaptation to Anoxemia, Am. J. Physiol. **109**:626, 1934.

24. Christie, R. V., and Meakins, J. C.: The Intrapleural Pressure in Congestive Heart Failure and Its Clinical Significance, J. Clin. Investigation **13**:323, 1934.

25. von Basch, cited by Lundsgaard, C.: Determination and Interpretation of Changes in Lung Volumes in Certain Heart Lesions, J. A. M. A. **80**:163 (Jan. 20) 1923.

26. McIntosh, C. A.: Respiratory Physiology in Thoracic Surgery, Ann. Surg. **102**:961, 1935.

27. Coryllos, P. N., and Birnbaum, G. L.: The Circulation in the Compressed, Atelectatic and Pneumonic Lung, Arch. Surg. **19**:1346 (Dec.) 1929.

cases (Nylin,[28] Bluhm[29] and Cournand, Bryan and Richards[30]) the volume of the blood and the blood flow must be greater in the uncollapsed lung, resulting in engorgement of the capillaries, which increases the rigidity of the lung and the alveolar air spaces, thus preventing collapse and increasing the volume of residual air. The ventilation (at rest) is the same after pneumothorax as before. Hence the ventilation of the uncollapsed lung must be doubled, thus ensuring a more uniform distribution of air throughout the lung (Meakins and Davies[20]). This improvement in alveolar ventilation by hyperventilation, however, will be curtailed to some extent by the impairment in pulmonary elasticity and distensibility (Christie and Meakins[24]).

Alterations in the Pulmonary Capacity in Patients with Lobar Pneumonia.—The observations presented indicate that the total and vital capacities are markedly reduced, while the amount of residual air may be slightly decreased or actually higher than the predicted values. The midcapacity is moderately reduced. The variability in the volume of the residual air in this acute infection is not surprising when one considers the numerous factors involved. Atelectasis, bronchial occlusion with obliteration of the alveoli, will tend to reduce the midcapacity and the amount of residual air. On the other hand, there are certain factors, such as pleuritic pain and general muscular weakness, that will prevent the thoracic cage and diaphragm from approaching their normal position at maximum expiration. Consequently, there will be a tendency for the volume of residual air to be increased. Although the process is unilateral, the opposite side cannot act wholly independently, so that even the volume of the healthy lung will be larger at the maximum expiratory position than normally. In three cases (W. A., C. M. and I. G.) in which we were able to obtain roentgenograms at maximum expiration both before and after the crisis, the area of the pulmonary fields was significantly greater during the height of the disease than during convalescence. In addition to these factors, changes in the parenchyma of the lung itself will influence the volume of the lungs at the midcapacity and maximum expiratory levels. Van Allen and Wu[31] have shown in experimental pneumonia that there is an increase in the elastic tension of the inflamed lungs. Our preliminary findings in

28. Nylin, G.: Untersuchungen über das Minutenvolumen des Herzens in 2 Fällen mit einseitigem künstlichem Pneumothorax, Beitr. z. Klin. d. Tuberk. **83**: 470, 1933.

29. Bluhm, I. L.: Working Test as Clinical Method for Determining the Function of the Lungs, Acta med. Scandinav., supp. 65, 1935, p. 1.

30. Cournand, A.; Bryan, N. A., and Richards, D. W., Jr.: Cardiac Output in Relation to Unilateral Pneumothorax in Man, J. Clin. Investigation **14**:181, 1935.

31. Van Allen, C. M., and Wu, C.: Increased Elastic Tension of the Lung in Experimental Pneumonia, J. Clin. Investigation **11**:589, 1932.

several cases of lobar pneumonia support their observations. These alterations, along with congestion of the capillaries in adjacent parts of the consolidated areas and anoxemia, will lead to "compensatory emphysema." All of these factors will likewise influence the other components of the total capacity.

The Respiratory Function in Cases of Lobar Pneumonia in Which Artificial Pneumothorax Was Given.—It has recently been shown that abnormally high values for the ratio $\frac{\text{residual air}}{\text{total capacity}} \times 100$ are associated with defective alveolar ventilation.[32] The increment in this ratio in patients with lobar pneumonia is an indication that there are underlying factors in the respiratory system which tend to interfere with proper pulmonary ventilation. Thus when pneumothorax is induced in a patient with this disease the affected lung, which is responsible for the derangement of the respiratory function, is compressed, and its effects are greatly minimized. If the lung is completely collapsed and the mean intrapleural pressure is kept positive, ventilation in the affected lung will be negligible, and breathing will be accomplished in a fairly normal manner by the contralateral lung, in spite of a greatly reduced pulmonary capacity. The present work has shown that the ratio $\frac{\text{residual air}}{\text{total capacity}} \times 100$, which may be taken as an index of pulmonary efficiency, approaches a more normal value after the institution of collapse. Furthermore, it has been shown by others (Means and Balboni [33]) that the only difference between a normal subject and a subject with a collapsed lung is that the latter when called on to increase the ventilation reaches his limit sooner than the former. The pulmonary reserve is great, and even though the components of the total capacity are reduced by more than half, the uncollapsed lung (at rest) is able to meet a threefold to fivefold increase in metabolism. If circulation and ventilation are parallel functions,[27] after the compression of the affected lung the major portion of the blood will be shunted from it to the aerated lung, thereby increasing the saturation of the arterial blood and conceivably reducing the absorption of toxins.

Little is as yet known of the rapidity with which these respiratory and circulatory adjustments in unilateral pneumothorax are made, but on the basis of available information concerning similar conditions, one is inclined to believe that the process, at least at first, is rapid. In

32. Hurtado, A.; Kaltreider, N. L., and McCann, W. S.: Studies of Total Pulmonary Capacity and Its Subdivisions: IX. Relationship to the Oxygen Saturation and Carbon Dioxide Content of the Arterial Blood, J. Clin. Investigation **14**:94, 1935.

33. Means, J. H., and Balboni, G. M.: The Various Factors of Respiration in Persons with Pneumothorax, J. Exper. Med. **24**:671, 1916.

experiments on animals Andrus [34] found that the blood content of the collapsed lung fell from 100 to 60 per cent during the first half hour. Prinzmetal [21] has shown that changes in intrapleural pressure and an increase in the capacity of the thoracic cage occurred several minutes after animals were exposed to high carbon dioxide and low oxygen tensions. Furthermore, in three normal subjects [23] it was found that the volume of residual air increased from 30 to 60 per cent after exposure to a barometric pressure of 419 mm. of mercury for sixty minutes. Likewise, there was marked dilatation of the capillaries and alveolar air spaces in the lungs of guinea-pigs exposed to the same pressure for two hours. These findings indicate that the circulatory and respiratory adjustments are in process soon after the etiologic factors are initiated.

From the experimental evidence available in the literature it is questionable whether there is an immediate increase in the oxygen content of the arterial blood after pneumothorax is rapidly induced. However, when one lung was collapsed slowly, Meakins and Davies [20] found that the arterial blood remained saturated throughout the course and when anoxemia was present prior to collapse therapy it was alleviated by it. Unfortunately thus far we have not had an opportunity to secure arterial blood before and after complete collapse in lobar pneumonia. A conclusion on this point awaits further investigation.

In the light of the foregoing considerations, when collapse therapy is given to a patient with lobar pneumonia he should obtain relief from the following symptoms: (1) pleural pain, (2) respiratory distress and (3) the long list of symptoms due to anoxemia. In numerous papers [35] dealing with artificial pneumothorax in the treatment of lobar pneumonia, most authors agree that these symptoms are ameliorated.

The readjustments after the induction of unilateral pneumothorax in lobar pneumonia are complicated because other factors besides respiration exert an influence on the lungs and lesser circulation. Until more clinical and investigative information on these cardiovascular and respiratory factors is available, one is not justified in drawing definite conclusions as to the effect on the cardiorespiratory system or the therapeutic value of the procedure. However, the information at hand suggests that artificial pneumothorax in cases of lobar pneumonia is a rational procedure from the point of view of respiratory function.

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34. Andrus, W. deW.: Observations on the Cardiorespiratory Physiology Following the Collapse of One Lung by Bronchial Ligation, Arch. Surg. **10**:506 (Jan.) 1925.

35. Klein, T., and Tuck, V. L.: Artificial Pneumothorax in the Treatment of Lobar Pneumonia, Am. Rev. Tuberc. **32**:511, 1935. Leopold and Lieberman.[2a] Blake, Howard and Hull.[2c]

SUMMARY AND CONCLUSIONS

Determinations of the total pulmonary capacity and its components and roentgenographic measurements of the expansion and size of the chest have been made for three patients with pulmonary tuberculosis who were given unilateral pneumothorax, for two patients with lobar pneumonia and for seven patients with lobar pneumonia during the induction of artificial pneumothorax. The gaseous content of the arterial blood was determined in eight of these cases. The results obtained led to the following conclusions:

The total and vital capacities and the midcapacity are proportionally reduced in a patient with unilateral pneumothorax of several months' duration. The volume of residual air is not diminished in proportion to the other capacities, resulting in an increase in the ratio $\frac{\text{residual air}}{\text{total capacity}} \times 100$.

The effect of posture on the pulmonary capacity of a patient with unilateral pneumothorax is similar to that found in normal subjects.

In a patient with pulmonary tuberculosis with unilateral pneumothorax the excursion of the diaphragm and the movement of the ribs are greatly reduced on the affected side.

Early in the course of lobar pneumonia the total and vital capacities are markedly reduced, while the volume of residual air may be only slightly decreased or actually higher than the predicted volume. The midcapacity is moderately reduced. As the disease progresses the absolute values are further diminished. Beginning several days after the crisis all the volumes gradually return to the predicted levels.

The ability to expand the chest is diminished during the early stages of lobar pneumonia, especially on the affected side. The size of the heart increases both in area and in transverse diameter during the febrile period and diminishes during convalescence.

The oxygen saturation and the carbon dioxide content of the arterial blood are reduced during the early stages of lobar pneumonia.

During the induction of artificial pneumothorax in cases of lobar pneumonia the total capacity and all its subdivisions (expressed as percentages of the predicted values) are proportionally reduced, resulting in a more normal relationship between the volume of residual air and the total capacity.

The height of the pulmonary field, measured on a roentgenogram, on the side of the pneumothorax and the area of the pulmonary field at maximum inspiration are increased during the period of maximum collapse.

The factors responsible for the alterations in the total pulmonary capacity and its subdivisions in lobar pneumonia and collapse therapy are discussed.

RENAL INSUFFICIENCY FROM BLOOD TRANSFUSION

I. RELATION TO URINARY ACIDITY

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From 1667, when the first blood transfusion was given to man by Jean Baptiste Denys,[1] until the discovery of hemagglutination by Landsteiner[2] in 1901 and the classification of blood groups by Janský[3] (1907) and Moss[4] (1910), hemoglobinuria was accepted as a common accompaniment of the injection of blood intravenously. In many of the patients who showed hemoglobin in the urine renal insufficiency developed, and death followed. Since testing the donor's and the recipient's blood for agglutination has become common, the incidence of severe complications from blood transfusions has, fortunately, greatly diminished. Hesse and Filatov[15a] reported a mortality of 1.3 per cent from 750 transfusions in Leningrad. They estimated that in general the mortality in various clinics was between 0.5 and 1.5 per cent. Tiber[5] (1930) reported 2 deaths from 1,467 transfusions (0.013 per cent) at Bellevue Hospital. Witts[6] described 3 deaths in 3,430 transfusions in Great Britain. Wildegans[7] placed the mortality from blood transfusions between 0.1 and 0.2 per cent.

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1. Denys, J. B., quoted by Keynes, G.: Blood Transfusion, New York, Oxford University Press, 1922.
2. Landsteiner, K.: Ueber Agglutinationserscheinungen normalen menschlichen Blutes, Wien. klin. Wchnschr. **14**:1132, 1901.
3. Janský, J.: Haematologische Studien bei Psychotikern, Klin. Sborn. 8: 85, 1907.
4. Moss, W. L.: Studies on Isoagglutinins and Isohemolysins, Bull. Johns Hopkins Hosp. **21**:63, 1910.
5. Tiber, A. M.: Observations on Blood Grouping and Blood Transfusion, Ann. Surg. **91**:481, 1930.
6. Witts, L. J.: Note on Blood Transfusion, Lancet **1**:1297, 1929.
7. Wildegans, H.: Die Bluttransfusion, Berlin, Julius Springer, 1933, p. 131.

Many of the deaths following blood transfusion are apparently due to renal insufficiency. There are many excellent descriptions of this syndrome in the literature. Commonly the transfusion is accompanied, or soon followed, by pain in the lumbar region or thighs, a feeling of constriction in the chest, chills and fever. Shock often occurs. Icterus may develop within a few hours. Hemoglobinuria is usually present. Partial or complete suppression of the urinary excretion may ensue, with consequent retention of nitrogen. When the renal function is impaired the patient usually dies in coma from four to fifteen days after the transfusion, although a few patients recover spontaneously. The recipient's serum has been proved to agglutinate the donor's cells in most instances, but no such incompatibility has been proved in some cases. Pathologic studies show that the principal organ affected is the kidney. There is interstitial cellular infiltration. The glomeruli are normal or dilated. The tubular epithelium shows various degrees of degeneration, while the lumens contain leukocytes, débris and masses of brownish pigment. Lindau [8] and Bordley [9] have presented excellent reviews of the recent literature. Lindau called attention to the similarity between the clinical and the pathologic picture of transfusion anuria and the anuric episodes occurring in blackwater fever. The relationship had previously been noted by Baker and Dodds.[10] Dudgeon [11] observed various degrees of renal damage in patients dying of blackwater fever, but Whipple [12] could not attribute any injury to hemoglobinuria per se in the patients he studied.

Our interest in this subject was stimulated by the occurrence in the University Hospital of two fatal cases of renal insufficiency following blood transfusion. These have been reported elsewhere.[13] As both our clinical experience and a review of the literature pointed to no promising therapeutic procedures in this condition, the problem was attacked experimentally.

As early as 1875 Ponfik [14] produced a somewhat similar clinical and pathologic picture in dogs by the injection of heterogenous blood.

8. Lindau, A.: Reaktionen nach Bluttransfusion: Eine ätiologische und pathologisch-anatomische Studie, Acta path. et microbiol. Scandinav. **5**:383, 1928.

9. Bordley, J.: Reactions Following Transfusion of Blood, with Urinary Suppression and Uremia, Arch. Int. Med. **47**:288 (Feb.) 1931.

10. Baker, S. L., and Dodds, E. C.: Obstruction of the Renal Tubules During the Excretion of Hemoglobin, Brit. J. Exper. Path. **6**:247, 1925.

11. Dudgeon, L. S.: Blackwater Fever, J. Hyg. **19**:208, 1921.

12. Whipple, G. H.: Pathology of Blackwater Fever, Am. J. Trop. Med. **7**:1, 1927.

13. DeGowin, E. L., and Baldridge, C. W.: Fatal Anuria Following Blood Transfusions: Inadequacy of Present Tests for Compatibility, Am. J. M. Sc. **188**:555, 1934.

14. Ponfik: Experimentelle Beiträge zur Lehre von der Transfusion, Virchows Arch. f. path. Anat. **62**:273, 1875.

Lévy [15] supplemented these observations by producing experimental hemoglobinuria in rabbits. He concluded that the excretion of hemoglobin produced the renal lesions. In 1911 Yorke and Nauss [16] reported that anuria and subsequent death could be produced by the intravenous injection of homogenous hemoglobin into rabbits fed on dry diets. This phenomenon did not occur when the animals were eating green food. The authors explained these results by postulating that the filtration pressure of the glomeruli was lowered by the low intake of fluid. Baker and Dodds,[10] however, challenged this explanation and produced experiments to show that the real difference lay in the fact that the rabbits in which renal insufficiency developed had acid urine, while those with alkaline urine were protected. They reported also in vitro experiments to show that solutions of hemoglobin were precipitated in acid solutions as acid hematin and that this reaction was augmented by the presence of more than 1 per cent sodium chloride. These authors considered that the pathologic and chemical picture could be entirely explained by the precipitation of hemoglobin in the tubular lumens in an acid solution with a high concentration of electrolyte, thus producing intrarenal obstruction.

Recent evidence has been introduced to show that renal ischemia may be an important factor in this problem. Mason and Mann [17] reported a transient decrease in the volume of the dog's kidney due to intravenous injections of hemoglobin. The glomeruli of the frog's kidney were observed to constrict under similar conditions. From the Scientific Institute for Blood Transfusion in Leningrad have come the reports of a series of studies by Hesse and his co-workers.[18] They have observed a

15. Lévy, L.: Untersuchungen über die Nierenveränderungen bei experimenteller Hämoglobinurie, Deutsches Arch. f. klin. Med. **81**:359, 1904.

16. Yorke, W., and Nauss, R. W.: The Mechanism of the Production of Suppression of Urine in Blackwater Fever, Ann. Trop. Med. **5**:287, 1911.

17. Mason, J. B., and Mann, B. F.: Effect of Hemoglobin on the Volume of Kidney, Am. J. Physiol. **98**:181, 1931.

18. (*a*) Hesse, E., and Filatov, A.: Experimentelle Untersuchungen über das Wesen des hämolytischen Schocks bei der Bluttransfusion und die therapeutische Beeinflussung desselben: I. Die Nierenfunktionsstörungen im akuten Experiment, Ztschr. f. d. ges. exper. Med. **86**:211, 1933. (*b*) Petroff, J.; Filatov, A.; Bogomolova, L., and Stroikova, X.: I. Die Pathogenese der Veränderungen des Herzens und der Gefässe, Arch. f. klin. Chir. **181**:209, 1934. (*c*) Wesselkin, P.; Lindenbaum, J., and Kartashevskiy, N. G.: II. Die Rolle des Zentralnervensystems in der Pathogenese der Gefäss-störungen beim hämolytischen Schock, ibid. **181**:227, 1934. (*d*) Iljin, W.: III. Experimentelle Beobachtungen der Nierentätigkeit nach Einführung von heterogenem und autohämolysiertem Blut, ibid. **181**:240, 1934. (*e*) Filatov, A.: Klinische und experimentelle Beiträge zur Reinfusion des in die Körperhöhlen ergossenen Blutes, ibid. **151**:184, 1928. (*f*) Hesse, E., and Filatov, A.: Neue praktische Ausblicke auf die Möglichkeit der Behandlung des hämolytischen Schocks bei der Bluttransfusion im Lichte experimenteller Forschung, Zentralbl. f. Chir. **59**:2674, 1932.

transient diminution in the renal volume and a fall in the systemic blood pressure following the injection into dogs of hemolyzed homogenous blood or whole human blood. The changes were more marked with the heterogenous blood and less marked with citrated blood which had been preserved for ten days. It was shown that the primary mechanism was the constricting action of the hemoglobin on the renal vessels themselves. Transfusions of compatible blood relaxed the spasm of the renal vessels and restored the function of the kidney. It was frequently possible to kill a dog with a single transfusion of human blood, but rarely did canine blood prove fatal. The dogs died two or three days after a transfusion, with mild retention of nitrogen and suppression of urine. The pathologic studies have not yet been published. The Russian workers have abandoned the theory that renal insufficiency is due to obstruction by precipitated hemoglobin. They have stated as their belief that the impairment of the renal function and the consequent pathologic changes can all be explained by spasm of the renal arteries and the resulting ischemia.

The injection of solutions of homogenous hemoglobin intravenously has been generally considered to be an innocuous procedure (Bayliss [19]). Havill, Lichty, Taylor and Whipple [20] demonstrated that hemoglobin is a threshold substance for the kidney of the dog and that it is probably excreted through the glomeruli, as the threshold is not changed when the tubules have been poisoned with mercury bichloride. Kerridge and Bayliss,[21] on the basis of perfusion experiments, concluded that proteins with a molecular weight greater than 68,000 do not filter through the glomeruli, while those of smaller size do. Hemoglobin, with a molecular weight of approximately 68,000, is a borderline substance and at times does filter through the glomerular membrane. Drabkin, Widerman and Landow [22] have recently shown by spectrophotometric analyses that when hemoglobin is injected intravenously into a dog, it rapidly disappears from the blood serum but that only about 10 per cent appears in the urine. It is excreted as hemoglobin, but on standing in contact with urine it is rapidly changed to methemoglobin.

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19. Bayliss, W. M.: Is Hemolyzed Blood Toxic? Brit. J. Exper. Path. **1**:1, 1920.

20. Havill, W. H.; Lichty, J. A., Jr.; Taylor, G. B., and Whipple, G. H.: II. Renal Threshold for Hemoglobin in Dogs Uninfluenced by Mercury Poisoning, J. Exper. Med. **55**:617, 1932.

21. Kerridge, P. M. T., and Bayliss, L. E.: Physiology of Proteinuria, Lancet **2**:785, 1932. Bayliss, L. E.; Kerridge, P. M. T., and Russell, D. S.: Excretion of Protein by Mammalian Kidney, J. Physiol. **77**:386, 1933.

22. Drabkin, D. L.; Widerman, A. H., and Landow, H.: The Fate of Hemoglobin Injected into the Blood Stream, J. Biol. Chem. **109**:xxvii, 1935.

METHODS

All the dogs used in our studies were kept in metabolism cages during the periods of observation so that voided urine could be collected. Catheterization was not performed, as we wished to avoid infection of the urinary tract as far as possible. Observations were usually made on twenty-four hour specimens to which toluene had been added. The volume, color and specific gravity were noted. Chemical tests were made for the presence of albumin, dextrose and hemoglobin. The centrifugated sediment was examined for casts, blood corpuscles and clumps of pigment. In our first experiments the reaction of the urine was tested with litmus paper. This proved not delicate enough, and later the approximate p_H was determined by a series of indicators, such as phenol red, bromthymol blue and bromcresol purple.

Blood was obtained from dogs which had been used for classes in surgical technic and had been under ether anesthesia for two hours. Blood was collected from the femoral arteries by means of paraffined cannulas and then defibrinated by being shaken in large Erlenmeyer flasks with bent wire paper clips. The defibrinated blood from several dogs was pooled and then centrifugated for forty-five minutes at 2,500 revolutions per minute, and the serum and the layer of leukocytes were drawn off with a pipet. The red blood corpuscles were not washed, as experiments reported in the literature of the innocuousness of serum did not seem to warrant the great amount of work entailed. The corpuscles were stored in a refrigerator usually for one day, occasionally longer, and then used. The cells were hemolyzed by being mixed with distilled water in the proportion of three parts of cells to four parts of water by volume. The solution of hemoglobin was injected into the jugular vein by gravity, the velocity being controlled so that it rarely exceeded 20 cc. per minute. The dogs were not anesthetized during the transfusion and, with few exceptions, seemed to suffer no inconvenience at the time. Specimens of blood for chemical analysis were obtained immediately preceding transfusion and at twenty-four-hour intervals thereafter until the death of the dog or until normal values for urea were attained.

Transfusions were given to each dog at intervals of from one week to several months, never being given more frequently. Care was taken to administer transfusions of the same pooled blood to as many dogs on alkaline diets as on acid diets. This served as a control on the toxicity of the blood from incidental causes. Postmortem examinations were performed as soon after death as possible, and routine histologic examinations were made of the kidneys, adrenal glands, liver, mesenteric lymph nodes, spleen, cardiac muscle, lungs and bone marrow from the femur.

EXPERIMENTAL OBSERVATIONS

So far, studies have been made on a series of twenty-eight dogs over a period of more than two years. Of this number, seven died of renal insufficiency following a tranfusion, two were killed when recovering from the same syndrome, three survived an episode of uremia, two died during a transfusion (apparently from speed shock), six died of an intercurrent infection, two were killed when in good health after many transfusions and one was discarded because it was ugly. Five are still living, the data being too insufficient to report in detail at this time.

Over one hundred transfusions of dog hemoglobin have been given. Most of the dogs showed no symptoms during the transfusion if the solution was administered slowly. The hemoglobin appeared in the urine

almost immediately in quantities sufficient to color it. The urine continued to be reddish for one or two days, and chemical tests showed the presence of hemoglobin for two more days. When there was no significant retention of nitrogen the dogs appeared well. A small amount of albumin occurred in the urine along with gross hemoglobinuria. Microscopic examination of the urinary sediment revealed various-sized masses of reddish brown pigment in the form of conglutinated globules. There were no casts or red blood corpuscles.

If retention of nitrogen occurred after a transfusion, the animal was less active than normal and soon began to vomit. It refused food but drank a large quantity of water, which was quickly regurgitated and seemed to serve as gastric lavage. If it did not recover, the course was clinically progressive, and the urea and creatinine values of the blood rose daily. A day before death the dog was so weak it could not stand. The muscles became somewhat rigid, and there was occasional twitching. Generalized convulsions were observed. A few hours before death the dog became comatose. Dogs died with this syndrome from four to ten days after a transfusion. The final values for the urea nitrogen of the blood varied from 119 to 362.6 mg. per hundred cubic centimeters and for creatinine from 4.6 to 15 mg. Occasionally some degree of alkalosis developed before an animal died, as determined by the carbon dioxide capacity and the chloride values of the plasma. When retention of nitrogen developed after a transfusion, the urinary sediment contained numbers of large casts composed of dense masses of brownish pigment. The maximum number was usually seen on the second day after the transfusion and were a reliable index as to whether retention of nitrogen was present in a given animal. These casts have been described as seen in rabbits and were photographed by Baker and Dodds.[10]

After a seemingly innocuous transfusion or after recovery from an episode of retention of nitrogen the urine is entirely normal, as judged by the specific gravity and the absence of albumin, dextrose, casts, hemoglobin pigments and erythrocytes.

Alkaline Diets.—Dogs seem to live normally and grow fat on vegetable scraps from the hospital kitchens. The entire dog colony of the medical college has been kept on this diet for years. Dogs 3, 4, 12 and 13 were kept on this diet and received from eight to fourteen transfusions of solution of dog hemoglobin without any deaths. Their protocols are summarized in table 1. Usually no significant rise in the urea content of the blood was noted. In dog 4, however, there was an appreciable retention of nitrogen after several of the earlier transfusions. We are uncertain as to the explanation for this, but it is possible that the dog was not eating and that the urine was slightly acid. The speci-

mens of urine were being tested for acidity with litmus paper at the time, a method that was later found to be inadequate. The protocol of dog 12, as set forth in table 2, is interesting. This animal was fed an alkaline diet over a period of eight months, but on several occasions it

TABLE 1.—*Data for Dogs on Alkaline Diets*

Dog	Sex	Weight, Kg.	Number of Transfusions	Hemoglobin Injected, Cc.*	Maximum Blood Values After Transfusion: Urea Nitrogen, Mg. per 100 Cc.	Maximum Blood Values After Transfusion: Creatinine, Mg. per 100 Cc.	Comment
3	♀	9.0	14	19.0	14.0	...	All urine alkaline
				27.7	18.2	1.0	
				15.0	16.8	1.0	
				14.0	57.4	3.3	
				16.6	57.4	2.5	
				13.3	39.9	1.5	
				16.6	53.9	1.2	
				6.6	18.2	1.1	
				14.4	15.4	1.0	
				16.6	29.4	1.2	
				16.6			
				16.6	37.1	1.2	
				14.0	21.0	1.2	
				16.6	20.3	1.2	Killed when in good health No nephropathy
4	♀	8.0	9	18.7	88.9	4.4	All urine alkaline
				14.4	113.4	5.0	
				7.5	74.9	5.0	
				15.0	59.5	3.0	
				18.7	50.4	1.2	
				18.7			
				18.7	76.3	3.4	
				15.6	51.1	2.2	
				18.7	60.9	2.7	Killed when in good health No nephropathy
12	♀	8.5	10	15.0	121.0	1.3	Urine acid
				8.0	23.8	1.2	Urine alkaline
				9.4	151.2	5.5	Urine acid
				10.0	26.0	1.0	Urine alkaline
				10.0	21.0	1.0	Urine alkaline
				8.6	26.6	1.0	Urine alkaline
				8.3	22.0	...	Urine alkaline
				12.0	27.0	...	Urine alkaline
				3.0	18.9	...	Urine alkaline
				12.0	133.7	4.4	Urine acid; killed Typical nephropathy
13	♀	16.0	8	15.0	20.3	1.1	All urine alkaline
				7.2	22.0	1.0	
				9.3	21.0	1.1	
				11.2	7.0	1.0	
				11.2	11.9	1.0	
				11.2	15.4	1.0	
				8.6	35.4	1.3	
				26.0	21.0	...	13 divided doses (daily)
				6.0	20.3	1.0	Living 3 months later

* The amount of hemoglobin injected is expressed in cubic centimeters of packed erythrocytes per kilogram of body weight before hemolysis.

refused to eat and the urine became acid. Transfusions while the urine was alkaline proved innocuous, but when hemoglobin was injected in the presence of acid urine, retention of nitrogen developed. While recovering from one episode of azotemia, the dog was killed, and the typical nephropathy associated with death due to renal insufficiency was

observed. Dogs 3 and 4 were killed after receiving fourteen and nine transfusions, respectively. No lesions were seen, except depositions of iron-containing pigment in the spleen, liver, lymph nodes and epithelial cells of the convoluted renal tubules.

Acid Diets.—Dogs were kept on diets consisting of cooked chopped beef, about ½ pound (225 Gm.) per day, with which was mixed about 8 Gm. of ammonium chloride. Beef alone often failed to make the urine

TABLE 2.—*Data for Dog 12 on an Alkaline Diet with Varying Urinary Reaction*

		Blood				
Date, 1935	p_H of Urine	Urea Nitrogen, Mg. per 100 Cc.	Creatinine, Mg. per 100 Cc.	Plasma Chlorides, Mg. per 100 Cc.	Carbon Dioxide Capacity, Vol. %	Weight 9 Kg.
2/23	6.8	13.3	1.0	675	49.0	Transfusion
2/25	...	11.9	1.0	625	41.0	
2/27	...	70.0	1.3	690	39.0	
3/ 2	6.8	121.0	1.3	550	50.0	Transfusion
3/ 7	...	23.8	1.2	625	62.0	
3/16	6.8	17.5	1.0	665	48.0	Transfusion
3/17	...	39.9	2.5	625	47.0	
3/18	...	89.9	3.5	612	48.5	
3/19	...	86.1	3.8	660	48.0	
3/20	...	119.0	4.3	640	38.0	
3/21	...	135.0	4.4	640	37.0	
3/22	...	151.2	5.5	...	....	
3/23	...	106.4	4.7	700	30.0	
3/24	...	114.8	4.4	600	38.0	
3/26	...	86.8	4.4	....	....	
3/28	...	56.0	....	....	....	
4/ 6	7.2	14.0	1.0	...	45.0	Transfusion
4/ 8	...	26.0	1.0	615	47.0	
4/13	7.0	12.6	1.0	625	....	Transfusion
4/15	...	21.0	1.0	...	....	
5/ 4	7.2	12.0	1.0	415	39.0	Transfusion
5/ 6	...	26.6	1.0	600	32.0	
10/13	7.4	13.0	1.0	452	28.0	Transfusion
10/14	...	22.0	1.0	419	36.0	
10/19	7.0	16.0	1.0	460	42.0	Transfusion
10/25	...	26.6	1.0	441	51.0	
11/11	7.8	18.2	1.0	...	35.2	Transfusion
11/12	...	18.9	1.1	...	48.5	
12/ 1	6.0	9.8	1.0	640	52.2	Transfusion
12/ 3	...	99.4	3.5	581	41.9	
12/ 6	...	123.9	4.8	...	37.2	
12/ 8	...	133.7	4.4	600	40.9	
12/10	...	117.0	4.6	690	42.8	Improving clinically; killed; typical nephropathy present

persistently acid. The dogs would not eat food which contained much more than 8 Gm. of ammonium chloride and occasionally refused this amount for several days at a time. The dogs usually held their weight on this diet and, while there was a tendency for the carbon dioxide capacity to become lower and for the chloride content of the plasma to become higher, this was not constant and remained within the limits of variation of the values for dogs on the alkaline diets.

We were naturally concerned with the effects of the diet itself on the renal function and pathologic picture. Neither albuminuria nor

cylindruria developed as a result of the diet alone. Of twenty-three dogs which had been on this diet for varying lengths of time up to five months, only in dog 8 did glycosuria develop at the end of three months. This disappeared when an alkaline diet was substituted and has not returned, although the acid diet has been resumed. Dog 7 died of speed shock during a transfusion, and although it had been on the diet continuously for four months, no histologic lesions were seen which could be attributed to the diet.

TABLE 3.—*Data for Dogs on Acid Diets*

Dog	Sex	Weight, Kg.	Number of Transfusions	Hemoglobin† Injected, Cc.	Maximum Blood Values After Transfusion: Urea Nitrogen, Mg. per 100 Cc.	Maximum Blood Values After Transfusion: Creatinine, Mg. per 100 Cc.	Comment*
1	♂	9.3	3	5.5	....	...	
				22.2	26.6	...	
				27.7	120.4	...	Died in coma 10 days after transfusion; typical nephropathy
2	♂	7.0	2	14.2	20.3	...	
				35.7	217.7	5.7	Died in coma 8 days after transfusion; typical nephropathy
5	♀	10.0	3	12.5	39.9	2.4	
				15.0	70.7	3.2	
				12.5	217.7	4.6	Died in coma 7 days after transfusion; typical nephropathy
10	♀	11.0	7	12.3	21.0	0.9	
				11.0	30.1	1.7	
				9.0	30.1	2.1	
				10.0	18.2	1.0	
				10.0	17.5	1.0	
				10.0	18.9	1.2	
				8.4	19.6	1.0	Living 3 months later
11	♀	10.0	2	8.0	16.8	1.0	
				11.4	350.0	12.5	Died in coma 4 days after transfusion; typical nephropathy
20	♀	11.4	1	9.0	119.0	5.3	Killed when recovering 5 days after transfusion; urea nitrogen 95.9 mg.; creatinine 3 mg.; typical nephropathy
21	♂	10.0	1	10.0	266.0	10.0	Died in coma 5 days after transfusion; typical nephropathy
8	♂	12.0	2	10.0	85.4	3.0	Survived
22	♀	11.0	1	9.5	81.9	3.5	Survived
23	♂	8.5	1	10.0	324.1	12.2	Died in coma 7 days after transfusion; typical nephropathy
24	♀	9.5	1	9.0	362.6	15.0	Died in coma 6 days after transfusion; typical nephropathy
26	♂	9.5	1	10.0	123.9	5.0	Survived

* All the specimens of urine were acid.
† The amount of hemoglobin injected is expressed in cubic centimeters of packed erythrocytes per kilogram of body weight before hemolysis.

Of the twenty-three dogs which received transfusions while on acid diets, seven died of renal insufficiency and one was killed when recovering. All showed the typical nephropathy, to be described. One dog received seven transfusions without effect and died later of intercurrent infection. The protocols of these are summarized in table 3. In dogs 20, 21, 23 and 24 retention of nitrogen developed after the first transfusion. The others died after two, two, three and three transfusions,

respectively. Dogs 7 and 19 died of speed shock. Dogs 9, 10, 13, 14, 15 and 16 died of intercurrent infection. Dogs 17 and 18 are still living, the data being insufficient to record at this time. The protocol of a typical dog on an acid diet is given in table 4.

Changes in Urinary Volume.—After transfusion there was generally diuresis during the first twenty-four hours. In only two dogs (dogs 11 and 21) was there suppression of urine after a transfusion, and in these cases there was anuria for the four and five days, respectively, elapsing between the transfusion and the death in coma.[23] In the other dogs

TABLE 4.—*Protocol of Dog 5 on Acid Diet*

	Urine					Blood		
Date, 1934	Volume, Cc.	Specific Gravity	Reaction	Albumin	Hemoglobin	Urea Nitrogen, Mg. per 100 Cc.	Creatinine, Mg. per 100 Cc.	
5/19	200	1.018	Acid	0	0	12.2	1.0	Transfusion
5/20	700	1.008	Acid	++	++++			
5/21	0	.....	.....	....	.....	28.0	2.4	
5/22	975	1.015	Alkaline	0	++			
5/23	0							
5/24	300	1.015	Acid	+	+			
5/25	650	1.015	Acid	Trace	Trace	39.9	1.6	
5/26	600	1.015	Acid	0	0			
11/17	100	.....	Alkaline	0	0	12.2	1.0	Transfusion
11/18	700	.....	Alkaline	++	++++			
11/19	500	1.006	Alkaline	+	+++	60.2	3.0	
11/20	400	1.010	Alkaline	+	+++			
11/21	600	.....	Acid	0	+	70.7	3.2	
11/22	0							
11/23	1,000	.....	Acid	0	Trace			
11/25	...	.....	.....	....	.....	47.6	1.3	
12/ 3	...	.....	.....	....	.....	28.0	1.1	
12/ 8	500	1.010	Acid	0	0	18.9	1.0	Transfusion
12/ 9	560	.....	Acid	++	++++	56.0	2.8	Vomiting
12/10	1,100	.....	Acid	+	+++	....	...	Vomiting
12/11	425†	1.006	Acid	0	++	150.6	5.0	Vomiting
12/12	550†	1.012	Acid	Trace	++	....	...	Vomiting
12/13	950†	1.008	Neutral	Trace	+	176.0	4.6	Vomiting
12/14	0	.....	.....	....	.....	....	...	Rigidity
12/15	900†	1.009	Acid	Trace	Trace	217.7	4.6	Comatose
12/16	Died in coma; typical nephropathy							

† The urine contained many casts of hemoglobin pigment.

that died of renal insufficiency the volume of urine excreted continued to be fairly high until death occurred. The amounts could not be accurately estimated because under the conditions of collection the urine was frequently mixed with vomitus.

Renal Vasoconstriction.—We made no direct observations of this phenomenon in our material. We doubt whether it was an important factor, however, because many of the dogs voided bright red urine

23. It is notable that of the dogs that died of renal insufficiency dog 11 had the most rapid death and high terminal values for the urea and creatinine contents of the blood.

containing hemoglobin immediately after the conclusion of a transfusion, and, as has been noted, there usually was diuresis during the first twenty-four hours.

Speed Shock.—Dogs 7 and 19 died on the table during a transfusion. While the solution of hemoglobin was running into the jugular vein, restlessness developed, with sudden dyspnea and convulsive movements. In dog 7 respiration and the heart beat stopped simultaneously. In dog 19 the heart continued to function for several minutes after respiration had ceased. Autopsy revealed nothing but a rather dilated heart and engorged jugular veins. An examination of the brain and spinal cord was not made, however. In the first case the velocity of the transfusion had been fast. In the second case the rate was 6 cc. of solution per minute. During the course of many transfusions it was observed that a velocity of over 20 cc. per minute frequently induced dyspnea and transient convulsive movements, which promptly disappeared when the velocity was decreased. Hirshfeld, Hyman and Wanger [24] described this syndrome and named it. They showed that it could be produced by the rapid intravenous injection of a number of unrelated substances, such as hypotonic, isotonic and hypertonic solutions, sugars, colloids and gels, suspensions and blood.

Repeated Transfusions.—Of the seven dogs that died of renal insufficiency, three died after one transfusion, two after two transfusions and two after three transfusions. There was no chemical evidence of an accumulative effect from previous transfusions. An experiment was set up to test this factor. Dog 13 was given an alkaline diet, and dog 15 was given an acid diet. Each received thirteen small daily injections of the same lot of dog hemoglobin. The dose was 2 cc. per kilogram of packed corpuscles hemolyzed with distilled water. These injections caused continuous hemoglobinuria for fifteen days. The urea and the creatinine content of the blood remained normal for both dogs.

Pathologic Examination.—A detailed study of the pathologic picture in human beings who died as a result of a blood transfusion and in the dogs which we used will be reported in another paper. In the dogs that died of renal insufficiency the significant lesions were confined to the kidneys. The glomeruli were normal. The lumens of the distal segments of the renal tubules were filled with brownish pigment that was closely packed and, in some places, in crystalline form. The pigment was so arranged as to block the tubules completely. The capillaries were engorged, and there was some interstitial leukocytic

24. Hirshfeld, S.; Hyman, H. T., and Wanger, J. J.: Influence of Velocity on the Response to Intravenous Injections, Arch. Int. Med. **47**:259 (Feb.) 1931.

infiltration. Some of the tubules were filled with leukocytes also. The tubular epithelium semed to be little damaged. The lesion appeared to be purely obstructive.

COMMENT

In our experiments the chemical studies of the blood and the pathologic picture of the renal lesions seemed to favor the explanation that renal insufficiency due to blood transfusion can be caused by precipitation of hemoglobin in the renal tubules and the production of insufficiency by obstruction. This is at variance with the theory of Hesse and his co-workers, which attributes the primary cause to vasoconstriction of the kidneys. We wish to point out some apparent differences between the syndrome produced in our dogs and that set forth in Iljin's [18d] report. In the Russian experiments whole human blood was injected into a series of nine dogs. Five survived and four died. These four all showed anuria and died two days after the transfusion, with relatively slight retention of nitrogen. Those surviving had temporary oliguria. Eight dogs were given a transfusion of their own hemolyzed blood. Seven survived, and one died in three days with an undetermined amount of retention of nitrogen. No mention is made of the type of diet or of the reaction of the urine. A report on the pathologic studies has not yet been published. In many cases the velocity of transfusion was much faster than that which we employed. From their protocols we have calculated that the average velocity of transfusion in the cases of the dogs that died was 35.7 cc. per minute. We were unable to give a solution of hemoglobin as fast as that without causing symptoms of speed shock. So it seems possible that the Russian workers are studying a different syndrome from the one we have here reported.

The fact that several transfusions have been required to produce renal insufficiency in many of our dogs can be given various interpretations. Since four dogs have shown retention of nitrogen, with the typical pathologic picture, after a single transfusion, the possibility of anaphylaxis is precluded. Renal lesions due to acidosis or alkalosis per se seem to be ruled out by our chemical studies. We choose to believe that there is still another factor besides urinary acidity which remains to be elucidated, and, when controlled, it will enable us to produce the syndrome more consistently.

At the time the present article was being written a paper appeared by Melnick, Burack and Cowgill [25] which reported a series of experi-

25. Melnick, D.; Burack, E., and Cowgill, G. R.: Development of Incompatibilities in Dogs by Repeated Infusions of Red Blood Cells, Proc. Soc. Exper. Biol. & Med. **33**:616 (Jan.) 1936.

ments in which dogs were repeatedly given transfusions of citrated blood from the same canine donors. Apparently very low titers of agglutinins and hemolysins in the recipients were increased after each transfusion, so that the results were clinically significant. We have not had time to study this phenomenon in relation to our work, but it should be pointed out that we used hemolyzed blood entirely, which was always pooled from three or four dogs and distributed among four dogs, and the syndrome produced that was due to renal insufficiency was unlike that ascribed to incompatible dog blood. The authors reported that no pathologic lesions were observed.

SUMMARY

When the urine is alkaline the intravenous injection of a large amount of dog hemoglobin into dogs seems to be innocuous. Under such conditions four dogs received a total of thirty-eight transfusions without harm. In one of the dogs retention of nitrogen developed on three occasions when the transfusion was given while the urine was acid.

When the urine is acid, transfusions of hemoglobin sooner or later produce renal insufficiency. Seven dogs died in coma from four to ten days after the transfusion, with the urea nitrogen values of the blood ranging between 120 and 362.6 mg. per hundred cubic centimeters and creatinine values between 4.6 and 15 mg. One dog was killed when recovering, the urea nitrogen content of the blood being 95 mg. Only one dog survived seven transfusions when on an acid diet. This syndrome, clinically and chemically, closely simulates that which develops in human beings with renal insufficiency resulting from hemoglobinuria.

From pathologic studies it appears that the cause of renal insufficiency resulting from hemoglobinuria in dogs is the obstruction of the tubular lumens with masses of pigment derived from hemoglobin.

These studies substantially confirm the experiments performed on rabbits by Baker and Dodds.[10]

Assistance was rendered by Dr. C. W. Baldridge before his death in an automobile accident on Nov. 22, 1934. Dr. H. P. Smith, professor of pathology, and Dr. R. B. Gibson, associate professor of biochemistry, gave advice on many matters. The members of the department of surgery made it possible for us to secure large quantities of dog blood.

CHANGING INCIDENCE OF TUBERCULOSIS OF THE TONSILS

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Numerous investigations have dealt with the incidence of tuberculosis in surgically removed tonsils. However, the majority of the earlier reports were based on relatively small series of cases or on selected cases, from which the true incidence of tuberculosis in surgically removed tonsils in all age groups, irrespective of the presence or absence of tuberculosis elsewhere, could not be determined.

Weller [1] was the first to report a series of sufficient length and nonselectivity to answer this question. The tonsils studied comprised the surgical material received as a routine in this laboratory during the years 1906 to 1919. The faucial and/or pharyngeal tonsils of 8,607 patients were studied, and the incidence of tuberculosis for the entire group was found to be 2.35 per cent.

As the literature previous to 1921 was comprehensively reviewed in that paper,[1] it will not be dealt with here. Since 1921 few series of sufficient size to be of value have been reported. Mullin [2] analyzed 400 tonsils and found the proportion with tuberculous infection to be 4.25 per cent, but it should be noted that in 60 per cent of his cases there was clinical evidence of tuberculosis elsewhere. MacCready and Crowe [3] found an incidence of 4.18 per cent in the examination of tonsils of 3,260 children. Howarth [4] found tubercles in 5 per cent of 100 tonsils of children from 3 to 15 years old. For a series of 200 patients in the same age group Scarff and Whitby [5] reported an incidence of 2 per cent.

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1. Weller, Carl V.: The Incidence and Histopathology of Tuberculosis of the Tonsils, Based on Eight Thousand Six Hundred Tonsillectomies, Arch. Int. Med. **27**:631 (June) 1921.

2. Mullin, W. V.: An Analysis of Some Cases of Tubercles in the Tonsil, J. A. M. A. **80**:1211 (April 28) 1923.

3. MacCready, P. B., and Crowe, S. J.: Tuberculosis of the Tonsils and Adenoids: A Clinical and Roentgen-Ray Study of Fifty Cases Observed for Five Years After Operation, Am. J. Dis. Child. **27**:112 (Feb.) 1924.

4. Howarth, Walter G., and Gloyne, S. R.: The Nature and Path of Infection in the Tonsils, J. Laryng. & Otol. **39**:429 (Aug.) 1924.

5. Scarff, Gordon R., and Whitby, L. E. H.: The Incidence of Tuberculous Infection in the Faucial and Pharyngeal Tonsils of Children, J. Laryng. & Otol. **43**:328 (May) 1928.

Wilkinson [6] and Rössner [7] have reported series which can be compared with those studied in this laboratory, since their cases were not selected but represented the routine examination of tonsils of subjects in all age groups. For 600 pairs of tonsils removed in 1900 Wilkinson found the incidence of tuberculosis to be 1.33 per cent, but only 0.5 per cent for 10,000 tonsils removed from 1923 to 1927. Rössner reported the diagnosis of tuberculosis in 1.01 per cent of 296 cases, the ages varying from 2 to 61 years.

In view of the decreased incidence of most forms of tuberculosis, particularly those of the respiratory tract, it became desirable to determine whether the incidence of tonsillar tuberculosis also has decreased in the material examined in this laboratory. Wilkinson [6] has shown such a change in the material at the Mayo Clinic. For this purpose the

Incidence of Tuberculosis in Tonsils, 1933 to 1935

Age Groups, Years	All Cases			Faucial Tonsils			Pharyngeal Tonsils		
	Number	Number of Tuberculous Tonsils	Incidence, %	Number	Number of Tuberculous Tonsils	Incidence, %	Number	Number of Tuberculous Tonsils	Incidence, %
0- 5	727	2	0.27	717	1	0.14	637	2	0.31
6-10	1,689	9	0.53	1,669	8	0.48	1,450	4	0.28
11-15	1,211	5	0.41	1,206	4	0.33	982	0	0.00
16-20	768	3	0.39	761	3	0.40	290	0	0.00
21-30	643	5	0.78	643	5	0.78	49	0	0.00
31-40	241	1	0.41	241	1	0.41	13	0	0.00
41-	263	1	0.38	263	1	0.40	12	0	0.00
Age unknown	817	2	0.24	817	1	0.12	430	1	0.23
Total	6,359	28	0.44	6,317	24	0.38	3,863	7	0.18

specimens obtained at 6,280 tonsillectomies, which were performed during the years 1933 to 1935, were reviewed, and the results were summarized in order to make them comparable to the series of 8,697 specimens studied prior to 1921 (Weller [1]).

The technic used in the preparation of these tonsils for microscopic examination was that outlined by Weller in 1921: fixation in solution of formaldehyde, bisection of the tonsil in a vertical plane at right angles to the mucous surface and microscopic examination of a section representing the entire cut surface, after the tissue had been embedded in paraffin and stained with hematoxylin and eosin. As was appreciated in 1921, there is an error in examining only one section of a tonsil, even

6. Wilkinson, H. Fielding: Pathologic Changes in Tonsils: A Study of Ten Thousand Pairs of Tonsils with Special Reference to the Presence of Cartilage, Bone, Tuberculosis and Bodies Suggestive of Actinomycosis, Arch. Otolaryng. **10**: 127 (Aug.) 1929.

7. Rössner, Therese: Häufigkeit und Bedeutung der Tonsillentuberkulose, Arch. f. Ohren-, Nasen- u. Kehlkopfh. **135**:214, 1933.

though it is an optimum section. The method employed, however, is the only one suitable for the routine examination of a large quantity of material.

The results of this study are summarized in the accompanying table, which is self-explanatory. The incidence of tuberculosis in the faucial tonsils in the various age groups showed some variation, the lowest (0.27 per cent) being in the youngest age group (0 to 5 years), while the highest (0.78 per cent) was found in the age period from 21 to 30 years. During the age period of 6 to 10 years tubercles were present in 0.53 per cent of cases. The other age groups showed a rather constant incidence of tonsillar tuberculosis, varying only from 0.38 to 0.41 per cent. No involvement of the pharyngeal tonsils was noted in subjects more than 10 years of age. The percentage of tuberculosis found in all tonsils and that in the faucial tonsils were very similar, 0.44 and 0.38 per cent, respectively, but the incidence of tuberculosis of the pharyngeal tonsils was very low, only 0.18 per cent.

A definite decrease in tonsillar tuberculosis was noted, the incidence for the years 1933 to 1935 being 0.44 per cent, as compared wtih 2.35 per cent for the years 1906 to 1919. Since these results were based on the comparatively large series of 6,359 and 8,697 cases, respectively, and since the methods of examination were exactly the same in the two groups, the results are highly significant. The trend toward a lower incidence, which Weller [1] noted (3 per cent in 1917 and 2.35 per cent in 1920), has continued to the present time. The reduced incidence of tonsillar tuberculosis was apparent in all age groups.

CHEST LEADS IN ELECTROCARDIOGRAPHY

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At first sight it seems surprising that the electrocardiogram was not derived precordially from the beginning, i. e., as directly as possible. However, the fact that it was not is not so strange, for the limb leads give almost constant pictures, while chest leads show distinct changes when the exploring electrode is shifted. Moreover, the standard leads of Einthoven are adequate for a study of arrhythmia, and the problem of irregularity of the pulse has for many years been the leading one in cardiology. Though chest leads were used occasionally in the early days of electrocardiography,[1] their value was not generally appreciated until electrocardiographic research was made subservient to examination of the myocardium, at first especially in coronary thrombosis. It is to the credit of Wood and Wolferth and their co-workers [2] to have shown in a number of papers that a fourth lead may sometimes supply information of value in the diagnosis of coronary thrombosis when the classic leads either are failing or do not give sufficiently obvious information.

However, not alone in coronary thrombosis do the three standard leads occasionally show a picture from which it is impossible to draw conclusions. In other disorders of the myocardium or of the coronary arteries the clinical picture, the evaluation of which should have the preference, can in the same way conflict with the electrocardiographic data.

From the Medical Clinic of the State University of Utrecht, Prof. A. A. Hijmans van den Bergh, director.

1. Einthoven, W.: Arch. internat. de physiol. **4**:132, 1906. Waller, A. D.: J. de physiol. **8**:229, 1887. Lewis, T.: Heart **7**:127 and 293, 1920; **8**:193, 1921. Ackermann, R.: Deutsches Arch. f. klin. Med. **144**:61, 1924.

2. (*a*) Wolferth, C. C., and Wood, F. C.: Am. J. M. Sc. **183**:30, 1932; M. Clin. North America **16**:161, 1932. (*b*) Wood, F. C., and Wolferth, C. C.: J. Clin. Investigation **11**:815, 1932; Experimental Coronary Occlusion, Arch. Int. Med. **51**:771 (May) 1933. (*c*) Wood, F. C.; Bellet, S.; McMillan, T. M., and Wolferth, C. C.: Electrocardiographic Study of Coronary Occlusion, ibid. **52**:752 (Nov.) 1933. (*d*) Wood, F. C., and Wolferth, C. C.: Am. Heart J. **9**:706, 1934. (*e*) Wolferth, C. C.; Wood, F. C.; Bellet, S., and Edeiken, J.: Tr. A. Am. Physicians **49**:223, 1934. (*f*) Wolferth, C. C., and Wood, F. C.: Acute Cardiac Infarction Involving Anterior and Posterior Surfaces of Left Ventricle, Arch. Int. Med. **56**:77 (July) 1935.

Since November 1933 we have as a rule used a chest lead in addition to the three standard leads. After having studied about one thousand, five hundred electrocardiograms obtained in this way, the value of such a "semidirect" lead in solving various electrocardiographic and clinical problems became evident. Thus the thoracic electrocardiogram, which often indicates damage of the myocardium by deviation of the T wave [3] in essential hypertension, chronic nephritis and coronary sclerosis, may teach new facts; [4] the question of the evaluation of the T waves in strong left or right axis deviation may be partly solved by the aid of the chest lead,[5] and finally this lead supplies data for a study of bundle branch and arborization block.[6]

TECHNIC

The greater part of our curves were taken in such a way that the right arm electrode was applied above the area of absolute dulness of the heart in the fourth intercostal space to the left of the sternum, while the left arm electrode was applied to the back, mesial to the inferior angle of the scapula. This lead corresponds more or less with lead IV of Wood and Wolferth, except that these authors applied the right arm electrode above the cardiac apex. Later we [4a] proceeded to apply the left leg electrode above the dulness of the heart and the right arm electrode to the left leg. Since the place of the nonexploring electrode is of little influence on the form of the electrocardiogram,[3] the same picture is obtained, except that it is a mirror picture with the P and T waves normally positive. Finally we applied the negative electrode on the left leg and the right arm electrode over the area of dulness of the heart, for it appeared to us that in the last lead but one several characteristics of deviating curves, especially in coronary thrombosis and in chronic nephritis, were less striking than in the inverted lead. In this last lead the P and T waves are therefore normally negative. All curves have been checked in such a way that 1 mm. equals 1 millivolt. Overshooting was prevented, while slackening did not exceed one fiftieth of a second.

1. THE NORMAL ELECTROCARDIOGRAM IN THE CHEST LEAD (FIG 1*A*)

As the figures found by us are practically the same as those reported by other investigators,[7] we shall not publish the tables referring to them. We believe, as will appear from what follows, that in the chest lead a negative or positive monophasic ventricular

3. Wilson, F. N.; Johnston, F. D.; Macleod, A. G., and Barker, P. S.: Am. Heart J. **9**:447, 1934. Footnotes 1 and 2.

4. (*a*) van Nieuwenhuizen, C. L. C.: Wien. Arch. f. inn. Med. **29**:25, 1936. (*b*) Master, A. M.: Am. Heart J. **9**:511 (April) 1934. (*c*) Katz, L. N., and Kissin, M.: ibid. **8**:595, 1933. (*d*) Goldbloom, A. A.: Am. J. M. Sc. **187**:489, 1934. (*e*) Bohning, A., and Katz, L. N.: ibid. **189**:833, 1935.

5. (*a*) Barnes, A. R., and Whitten, M. B.: .Am. Heart J. **5**:142, 1929. (*b*) van Nieuwenhuizen, C. L. C., and Hartog, H. A. P.: ibid., to be published.

6. Wilson, F. N.: Heart **16**:155, 1933.

7. Master,[4b] Katz and Kissin.[4c] Goldbloom.[4d] Bohning and Katz.[4e]

complex which is too broad or the failing of the Q or of the R wave is just as pathologic as a difference of level between the ST and the PQ segment greater than 2.5 mm. or a flat diaphasic or inverted T wave, except in a long sheep heart or the heart of a child (see section 3). Sometimes clinical importance must be attached to the origin of a flat or diphasic P wave.

CHANGES DUE TO CORONARY THROMBOSIS

Wood and Wolferth [2c] divided the tracings obtained by them in this disease into two groups. In the first group—tracings divided thoracicly in anterior infarctions—the electrocardiogram shows a difference of level between the depreciated ST segment and the iso-electric line, which is larger and remains longer than in the other leads. In the course of time a positive T wave arises. The Q wave is either absent or very small. Usually it appears that the RS-T segment in lead I runs higher than normal; sometimes the RS-T segment in lead III lies lower than normal. In the second group—tracings in posterior

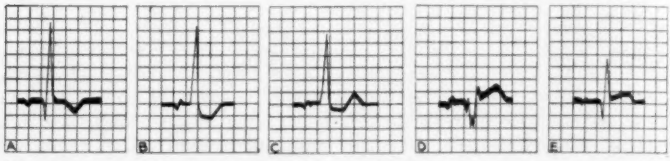

Fig. 1.—*A*, a normal electrocardiogram; *B* and *C*, the C 2 type of tracing; *D* and *E*, the C 1 type of tracing.

infarctions—the electrocardiogram does not properly show a typical deviation in the chest lead. Sometimes there is a slight difference of level between the ST segment and the iso-electric line, and sometimes there is a flat or positive T wave. The deviations should be searched for rather in lead II, where the ST segment is nearly always elevated and a negative T wave arises in the long run; in lead III a deep Q wave usually is seen which satisfies the criteria fixed by Pardee.

However, in our opinion a depression in the course of the RS-T interval in the chest lead cannot be considered a characteristic of coronary thrombosis, as the same deviation may be seen in coronary sclerosis, essential hypertension and chronic nephritis. Neither is a positive T wave a typical feature, as it is seen in many deviations of the myocardium. Wood and Wolferth [2d] have described the occurrence of very high T waves in the thoracic electrocardiogram, which, remarkably, were found especially in cases of mild involvement. We too saw this peculiarity several times (see the case reports which follow), though it is an open question whether such high T waves would not be found

more often in the course of coronary thrombosis if the surface of the chest were accurately explored with the electrode.

Finally, Wood and Wolferth and their colleagues [2c] pointed to the importance in the diagnosis of coronary thrombosis of a small deflection directed upward at the beginning of the ventricular complex. However, we saw this "initial upward deflection" also in cases in which coronary thrombosis could be ruled out.

Referring to our own material, the thoracic electrocardiograms obtained in cases of coronary thrombosis may be divided into the two following types, which we call the C 1 and C 2 types: [8]

1. The C 2 type (fig. 1 *B* and *C*). This type, which to a certain extent resembles that of the first type described by Wood and Wolferth, has for its particularity *a flat or slightly concave descending ST segment, proceeding at a pronounced angle (usually 125 or 130 degrees) into an ascending line,* which continues into a positive T wave or in the iso-electric line. The ST line may run far under the iso-electric level but also may rise from it. The positive T wave may be lacking, though it usually appears in the course of the disease. The Q summit may be missing, but sometimes it is obvious. The P summit is sometimes negative before thrombosis occurs and diphasic afterward. A notch in the ventricular complex is sometimes missing in the lead used by us; but if the cardiac region is explored with the anterior electrode, it is usually found. In the course of coronary thrombosis a high T wave in the chest lead and also in leads II and III may appear in connection with this type of thrombosis. Usually an acute stage of pain, anxiety or dyspnea was noted in the history of a patient with this type of electrocardiogram, and often there was a long history of angina pectoris. Once this type of tracing was found in a case of diabetes mellitus and syphilis (case 4, table 1).

It is important to retrace changes in the standard leads that are typical of coronary thrombosis and to observe what localization they admit. Three times a W-shaped ventricular complex occurred in lead I; twice a Pardee Q wave occurred in lead III. The W-shaped ventricular complex acquired a sharp negative T wave after some time, and the Pardee Q wave remained. In the four other cases no characteristic alterations were seen; *thus the thoracic lead offered here the only secure electrocardiographic diagnostic evidence.*[8a]

According to Barnes and Whitten [5] the sharp negative T wave in lead I which follows the stage of the W-shaped complex must be

8. The types are described for the right arm electrode (heart dulness) and the left leg electrode.

8a. Since the preparation of this article this view has been confirmed. Especially in cases of mild coronary thrombosis, lead IV often offers the only deviations.

ascribed to anterior infarction, which corresponds with our view that the C 2 type is characteristic of infarction in the anterior wall.[8b] On the other hand, according to Wilson [6] the occurrence of a Pardee Q wave in lead III (Q III type) is characteristic of infarction of the posterior wall, which is in contradiction with our experiences with curves of this form. Nevertheless, one must be very careful when judging a Pardee Q wave. When this picture is seen to arise (e. g., together with violent substernal pain), this is of far greater value than a deep Q wave in lead III that is already present, which may occur also in coronary sclerosis without myocardial infarction (Willius [9] and Pardee [10]).

2. The C 1 type of tracing (fig. 1 *D* and *E*). This type, which up to now has not been described in the literature on chest leads, exists in its most perfect form (fig. 1 *D*) in the ventricular complex in which are notable an *"initial upward deflection"; a deep Q wave, a notch in the Q wave and especially an ST line with a high take-off that goes on convexly and into which creeps the T wave.* Unlike the C 2 type, this type as a rule shows a pronounced Q wave. The small notch directed upward may be missing, but it may occur in the C 2 type and may therefore be valued only in connection with the other deflections. The most characteristic point is the high and convex course of the RS-T segment as it is seen in anterior infarction in lead I, but usually it is less definite. In other cases the ST segment becomes flat but keeps on rising too high and runs above the iso-electric level (fig. 1 *E*). As a rule the following more or less typical alterations are found in the other leads:

Lead I. An absolutely or relatively too deep S wave and a low T wave.

Lead II. A too broad ventricular complex, notches in R, S or RS and a too deep S wave; the PQ distance is always too long.

Lead III. A too deep S wave, notches after the S wave, a flat diphasic or negative T wave and sometimes a Pardee Q wave, a high take-off of the convex ST segment (Pardee RS-T wave) or a W-shaped or M-shaped ventricular complex.

It is notable that in the history of patients who show electrocardiograms of this type an acute moment is usually missed and that sometimes (case 5, section 1) the alterations are seen to arise gradually in the course of time. It is our opinion that these electrocardiographic

8b. Afterward in three other cases the postmortem examination proved the diagnosis to be correct.

9. Willius, F. A.: Deutsches Arch. f. klin. Med. **172**:113, 1931.

10. Pardee, H. E. B.: An Electrocardiographic Sign of Coronary Artery Obstruction, Arch. Int. Med. **26**:244 (Aug.) 1920.

alterations are probably due to posterior infarction. In favor of that theory the following reasons may be cited:

1. Alterations typical of coronary thrombosis are seen in the other leads, especially in lead III, which indicates posterior infarction, according to Barnes and Whitten and to Wilson.

2. The broad ventricular complexes, which have approximately the shape of an arborization block, and the lengthened or maximal atrioventricular conduction time, which are *always* found in this form, must be ascribed, as far as our knowledge goes, to alterations in the circulation of the posterior coronary artery.[11]

3. A negative reason is the absence of deviations characteristic of coronary thrombosis in lead I.

4. About the same form is sometimes seen in ventricular extrasystoles in the chest lead, when ventricular systoles of the left type exist in leads I and III (fig. 4 *E*).

It is possible that in some such manner as is herewith suggested the problem of anterior infarction, which usually occurs suddenly, and posterior infarction, which usually appears gradually as the result of increasing coronary sclerosis, concerning which there is considerable controversy, may be settled. Clinicians have always had the impression that anterior infarction occurs much oftener than posterior infarction, whereas many workers in pathologic anatomy have found an equal division of thrombosis of the left and of the right coronary artery. Perhaps posterior infarctions escape clinical observation; an attack of dyspnea or a moderate attack of angina pectoris may be caused by coronary thrombosis. There is no certainty about it, however, as none of the patients have died and postmortem inspection has not been possible.[11a] According to other writers (Wood and Wolferth and Jervell) posterior infarction does not supply typical data. According to them it is only by means of the chest lead, which is indeed "semidirect," that alterations of the anterior parts of the heart and especially of the cardiac apex (which is situated nearest to the electrode) become electrocardiographically visible. On the other hand our patients, though not showing the extensive typical picture of coronary thrombosis, were suspected of having it; and in connection with the C 1 type we found typical pictures only in the third standard lead. Finally, it is possible that the C 1 type is caused by septal infarction, due to insufficiency of either the left or the right coronary artery. In the first case anterior

11. Spalteholz, W.: Verhandl. d. anat. Gesellsch. **21**:141, 1907. Jamin and Merkel: Die koronar Arterien des menschlichen Herzens, Jena, Gustav Fischer, 1907. Hans: Anat. Hefte **43**:627, 1911. Taterka, H.: Klin. Wchnschr. **5**:1833, 1926. Frank: Ztschr. f. Kreislaufforsch. **21**:664, 1929.

11a. Lately in a case of acute posterior infarction (confirmed) a similar curve was found (Q wave of 20 mm.; a very high take-off of the convex ST segment).

infarction of the septum should arise, with possible infarction of parts of the left ventricle and of the apex; in the second case posterior infarction of the septum should arise, with or without infarction of the right ventricle. Considering the deviations in the other leads, we believe

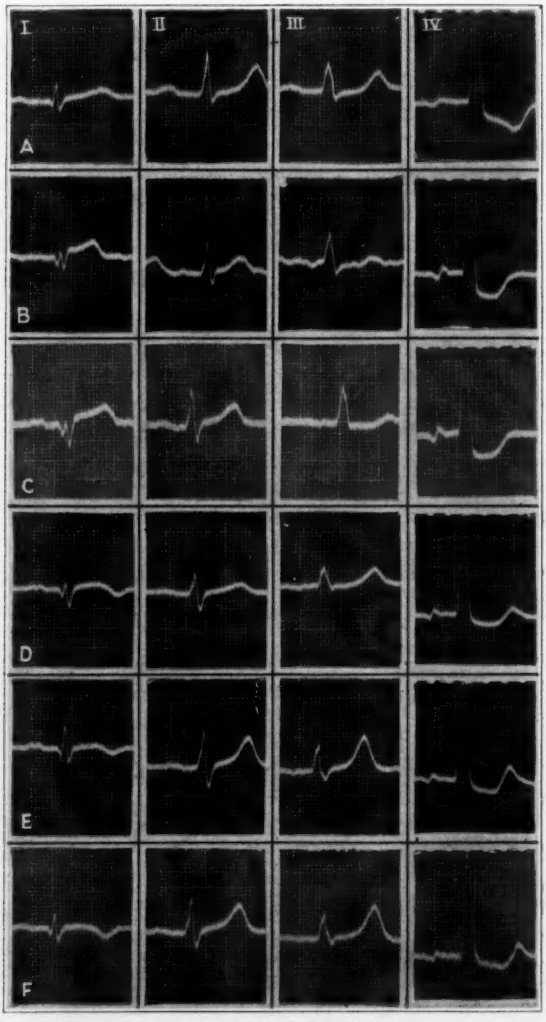

Fig. 2.—Examples of the C 2 type of tracing in case 1, section 1 (table 1, case 1). *A* was taken on Jan. 30, 1934, *B* on February 2, *C* on February 3, *D* on February 12, *E* on May 1 and *F* on April 7, 1935.

that the C 1 type is the expression of infarction of the posterior wall of the heart or perhaps in the posterior part of the ventricular septum.

On one occasion we saw a C 1 type, though a less obvious one, in a case of rheumatic myocarditis (case 7, table 2; fig. 6 *D*).

In summary, two deviations of the thoracic electrocardiogram are described which are typical of anterior infarction (the C 2 type), on the one hand, and most probably of posterior infarction (the C 1 type), on the other. If the W-shaped ventricular complex in lead I is considered to be typical electrocardiographic evidence of anterior infarction and if the occurrence of it in lead III is considered to be characteristic of posterior infarction, then in eight of fourteen cases the diagnosis was established with the standard leads. In six cases the chest lead offered the only pathognomonic evidence, and in several cases the thoracic electrocardiogram was typical when in the course of the disease the standard leads became more and more normal. The following cases are illustrative.

CASE 1 (table 1, case 1; fig. 2 *A* to *F*).—A bookkeeper aged 52, who had never been seriously ill before, suddenly had an attack of violent pain in the cardiac region. At his own request he was taken immediately to the hospital, where a diagnosis of coronary thrombosis was made. During his stay he recovered entirely. An electrocardiogram made half an hour after the beginning of the initial attack (fig. 2 *A*) showed some deviations in the course of the RS-T interval in the three standard leads; these, however, were not typical. In the chest lead the C 2 type was seen. After forty-eight hours a W-shaped ventricular complex was noted in lead I, with an arcuate ST segment (fig. 2 *B*). Later a negative T wave arose, which in the course of sixteen months returned to a flat T wave (fig. 2 *C* to *F*). In leads II and III the T waves became very high after fourteen months (fig. 2 *E*). Finally the ST segment took off iso-electrically in lead IV, but its course remained typical of the C 2 type; in the meantime typical changes were no longer seen in the other leads. This case proves that in very early stages the chest lead may be the only electrocardiographic sign of coronary thrombosis. It proves also that the unchangeable characteristic lies in the course of ST and not alone in the take-off of ST or in a positive T wave.

CASE 2 (table 1, case 5; fig. 3 *D* to *E*).—Two days prior to his admission to our clinic a mason aged 43 had a sudden pain in the chest. When he was admitted to the clinic the pulse rate was 88 and the temperature 38 C. (100.4 F.); but most striking was the violent dyspnea. On percussion the heart appeared to be dilated somewhat to the left. For several hours slight pericardial friction was heard. Swallowing was painful. The differential diagnosis lay between coronary thrombosis and diaphragmatic pleuritis. The roentgenogram did not indicate an existing pleuritis, but there were deviations in the electrocardiogram. A Pardee Q wave warned us to be careful and in lead IV a C 2 type appeared to be present, with a deep Q wave (fig. 3 *D*). The man soon recovered and was discharged at his own request. Probably pericardio-pleuritis was the correct diagnosis, with pleuritis the cause of the most serious complaints. This case teaches the value of the chest lead in making a difficult differential diagnosis in a case of acute intrathoracic disease. Thus there was found, besides the electrocardiographic characteristics of anterior infarction, a very deep Q wave in lead IV. Theoretically it is possible that this last-mentioned deviation existed as the remainder of posterior infarction; absolute certainty could of course not be obtained.

TABLE 1.—*Data for Patients Included in Section One with C 2 Type of Tracing*

Case	Sex	Age	Deviations in Lead I	Deviations in Lead II	Deviations in Lead III	Deviations in Lead IV	Diagnosis and Comments
1	M	52	W-shaped QRS complex	ST aniso-electric; high T waves occurred later	Notches; high T waves later	C 2 type	Coronary thrombosis (case 1, section 1; fig. 2 A to F)
2	M	43	W-shaped QRS complex	No typical deviations	ST marked aniso-electric	C 2 type	Coronary thrombosis (fig. 3 A)
3	M	62	T diphasic; R 19 mm.	R low; notch in RS	Deep S	C 2 type	Coronary thrombosis; 4 years ago severe substernal pain; same complaints 14 days ago (fig. 3 B)
4	M	64	T deep inverted; R 18 mm.	T negative; notch in RS	S too deep	C 2 type	Diabetes mellitus; progressive paralysis (case 5, section 1; fig. 3 C)
5	M	43	ST aniso-electric	Notch in R	Pardee Q	C 2 type	Coronary thrombosis (case 2, section 1; fig. 3 D and E)
6	M	42	T negative, diphasic	T diphasic	Notch in RS-T flat	C 2 type	Syphilitic aortic regurgitation (?); coronary thrombosis (case 3, section 1)
7	M	56	ST aniso-electric; T negative	T deep, inverted	Pardee Q; T deep inverted	C 2 type	Chronic articular rheumatism; attacks of pain in left and right arm last month; coronary occlusion ?
8	M	65	ST aniso-electric; T flat	T diphasic	Queer QRS complex	C 2 type	Coronary thrombosis; 14 days after attack of severe substernal pain
9	M	52	Low W-shaped QRS complex	ST aniso-electric	ST aniso-electric	C 2 type	Coronary thrombosis (case 4, section 1; fig. 4 A to D)
10	F	38	T low; ST aniso-electric	T low; ST aniso-electric	T diphasic	C 2 type	Coronary thrombosis ? (severe attack of substernal pain several months ago)
11	M	59	T trace	No deviation	ST high take-off	C 2 type	Coronary thrombosis 2 months ago; angina pectoris last year
12	M	55	W-shaped ventricular complex	Notch in R	Small ventricular complex; T low	C 2 type	Coronary thrombosis 4 months ago; since then dyspnea on exertion

CASE 3 (table 1, case 6).—A man aged 42 had been complaining for six weeks of pain in the right arm and palpitation on exertion. Ten days prior to his admission to the clinic he suddenly had a violent pain in the abdomen, the temperature rose and he sweated profusely. Three years before he had been in a hospital, and a diagnosis of syphilitic aortic insufficiency had been made (the Wassermann reaction of the blood was + 4, and the Sachs-Georgi test was positive). On

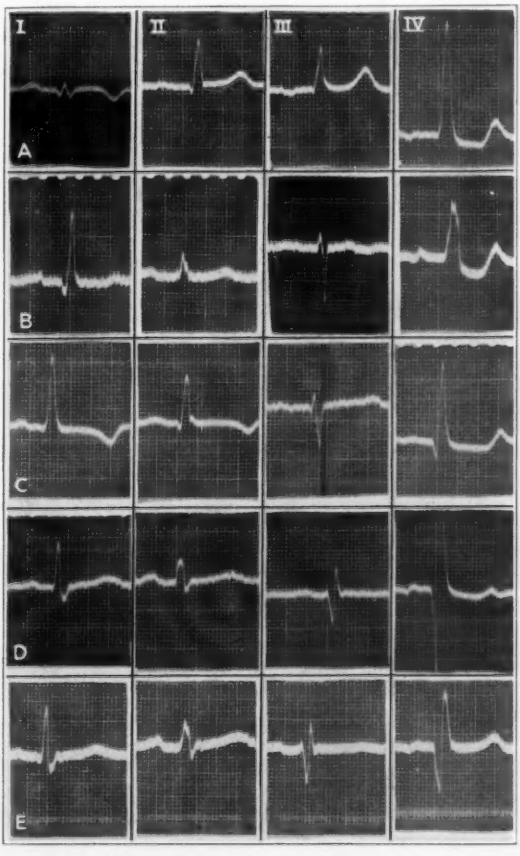

Fig. 3.—Examples of the C 2 type of tracing. For data on *A* see table 1, case 2; for *B* see table 1, case 3; for *C* see case 5 (section 1) and table 1, case 4; for *D* and *E* see case 2 (section 1) and table 1, case 5.

examination the following conditions were diagnosed: aortic insufficiency and cerebrospinal syphilis (the Wassermann and Sachs-Georgi reactions being negative). The pulse rate was 84, the temperature 37.7 C. (100 F.) and the respiratory rate normal. The sedimentation rate of the erythrocytes was normal. There were

7,200 leukocytes. No pericardial friction was heard. On the basis of this information it was not possible to make a diagnosis of coronary thrombosis. Sixteen days after the attack of pain in the abdomen an electrocardiogram showed a diphasic T wave in leads I and II and a C 2 type in the chest lead. Here too a distinct Q wave was seen in lead IV, which did *not* have the shape of the Q wave typical of posterior infarction (see C 1 type). Did it arise at the time of the attack of pain in the abdomen, and was it connected in any way with it? Did infarction

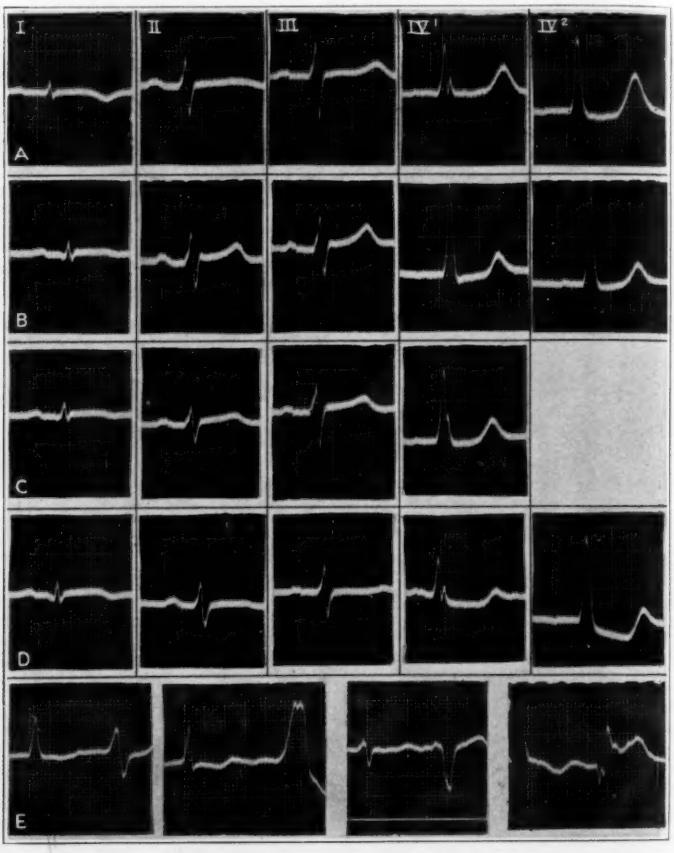

Fig. 4.—Examples of the C 2 type of tracing. For data on *A* to *D* see case 4 (section 1) and table 1, case 9. *A* was taken on Aug. 2, 1935, *B* on August 6, *C* on August 8 and *D* on August 13. For lead IV ¹ the anterior electrode was placed over the fourth interspace, 4 cm. to the left of the sternum. For lead IV ² the anterior electrode was placed over the cardiac apex. *E* shows the C 1 form of tracing in an extrasystole as compared with ventricular extrasystoles of the left axis type in standard leads.

arise stealthily as a consequence of coronary stenosis caused by syphilis of the aorta? The answer cannot be given on the basis of the electrocardiogram. Nevertheless this case illustrates the value of the chest lead when making a diagnosis of myocardial infarction when there are indistinct clinical symptoms and the results of other methods of examination are not of great value. Moreover, it shows that in making a diagnosis of myocardial infarction the disappearance of the Q wave in the chest lead is not obligatory.

CASE 4 (table 1, case 9; fig. 4 *A* to *D*).—A workman aged 52, who had never been ill before, had a sudden violent pain in the cardiac region and in the upper portion of the abdomen while riding a bicycle. One day after his admission to the hospital there was a distinct *défense musculaire* in the upper portion of the abdomen. The pulse rate was not accelerated. The temperature was 38.7 C. (101 F.). The sedimentation rate of the erythrocytes had increased (48 mm. after one hour and 96 mm. after two hours, according to Westergren's method). Though there was a possibility that an acute abdominal condition was present, the diagnosis was thought to be coronary thrombosis on account of the clinical picture. In lead I the electrocardiogram showed a W-shaped ventricular complex and in leads I, II and III a difference of level between ST and PQ and an aniso-electrical course of ST. With the chest lead there was a C 2 type of tracing. In the course of the illness a high T wave arose in the chest lead when the electrode was applied distally from the apex (IV^2). In order to see a distinct notch in the R wave the electrode had to be placed in the fourth intercostal space above the left margin of the area of dulness of the heart. Electrocardiograms made later showed an iso-electrical beginning of the ST segment, but the same course, as described, remained.

CASE 5 (table 1, case 4; fig. 3 *C*).—A man aged 64, suffering from diabetes and dementia paralytica, had complained for about a year of dyspnea on exertion. For three weeks there had been a vague pain in the upper portion of the abdomen on moderate exertion. On examination he appeared to have a cor bovinum. Roentgenograms revealed marked dilatation of both ventricles and great congestion of the lungs. An electrocardiogram showed distinct left axis deviation; in lead I the T wave was negative, in lead III positive and in lead II negative again. With lead IV there was a C 2 type of tracing. The anamnesis and the clinical examination revealed no sign of myocardial infarction, but we felt justified in considering that in the presence of diabetes and tertiary syphilis chronic coronary insufficiency had caused infarction. How far syphilis of the myocardium was responsible for the picture seen in the thoracic electrocardiogram must be left undecided. In view of the fact that in many other cases in which there was syphilitic aortic regurgitation with anginal complaints a C 2 type of tracing was not seen, the importance of syphilis of the myocardium is not considered to be very great in this case.

CASE 6 (table 2, case 1; fig. 5 *A*).—Half a year prior to clinical observation this man aged 65 was suddenly seized one night with severe dyspnea. After that he tired easily and had palpitations on slight exertion. He never had pain. On examination there was hypertension, and the heart was greatly enlarged to the left and to the right. There was strong cardiac congestion, and the liver was enlarged. An electrocardiogram showed a broad ventricular complex with a deep S wave in all leads (also in lead I, where a failing of S and a very high R might be expected on account of the hypertension). In lead II a distinct notch was seen and a slurring of the RS segment, the same as in lead I. With the chest lead there was the characteristic C 1 type of tracing. In our opinion the electrocardiogram pointed to the existence of myocardial infarction. There was no positive proof

TABLE 2.—*Data for Patients Included in Section One with C 1 Type of Tracing*

Case	Sex	Age	Deviations in Lead I	Deviations in Lead II	Deviations in Lead III	Deviations in Lead IV	Diagnosis and Comments
1	M	65	S too deep; T low	Broad QRS complex; A-V conduction time 0.2 sec.; notches	Broad QRS complex	C 1 type	Coronary thrombosis (case 6, section 1; fig. 5 A)
2	M	65	S too deep; T low	A-V conduction time 0.2 sec.; notches	Pardee Q; T trace	C 1 type	Coronary thrombosis ? (case 7, section 1; fig. 5 B)
3	M	51	S too deep; T low	A-V conduction time 0.2 sec.; notch in RS	Broad complex; T negative; notches	C 1 type	Aortic regurgitation and aneurysm; coronary stenosis (case 8, section 1; fig. 5 C)
4	M	69	S too deep; T low	A-V conduction time 0.19 sec.; notch in R; T diphasic	Slight W-shaped complex	C 1 type	Coronary thrombosis (case 9, section 1; fig. 5 D and E)
5	F	70	ST 3 mm. lower than PQ; T diphasic; ST concave	Small QRS complex; ST concave; notch in R	"Pardee RS-T"; deep S	C 1 type	Gradually increasing coronary sclerosis (case 10, section 1; fig. 6 A to C)
6	M	70	S too deep; broad QRS complex	A-V conduction time 0.2 sec.; S too deep; notch after S	S too deep; ST anisoelectric	C 1 type	Coronary thrombosis 8 days previously (fig. 6 E)
7	F	19	S too deep; T diphasic; notch in RS	ST concave	Notch in R; T diphasic	C 1 type	Acute polyarticular rheumatism; pericarditis (case 11, section 1; fig. 6 D)

that it arose at the time of the first attack of oppression through coronary thrombosis or, which seems more probable to us, gradually as a result of coronary sclerosis.

CASE 7 (table 2, case 2; fig. 5 *B*).—This man aged 65 had an interesting history. On Jan. 7, 1932, he suddenly had a violent pain in the left side which radiated to the upper portion of the abdomen; this pain lasted for a day and a half. He was short of breath, and deep breathing was painful. His physician considered

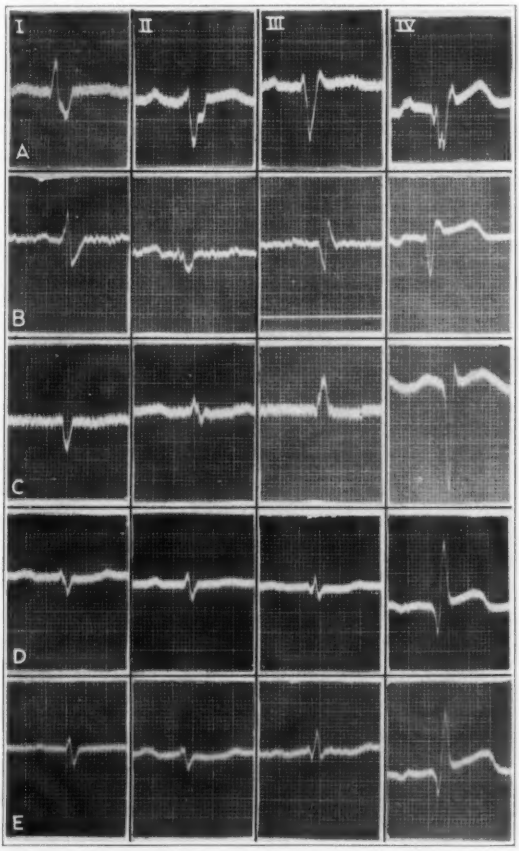

Fig. 5.—Examples of the C 1 type of tracing. For data on *A* see case 6 (section 1) and table 2, case 1; for *B* see case 7 (section 1) and table 2, case 2; for *C* see case 8 (section 1) and table 2, case 3, and for *D* and *E* see case 9 (section 1) and table 2, case 4.

that he had heart disease. After some time pleuritic friction became audible, and he was sent to our clinic, the diagnosis being pleuritis. At the time of admission to the clinic he had a slight fever (temperature of 38.2 C., 101 F.), the respiratory

rate was 26 per minute and the pulse was slightly unequal and irregular, with a rate of 108. The blood pressure was 140 systolic and 90 diastolic. At the base of the left lung there was slight pleuritic friction, with pericardial friction of the heart, which was somewhat dilated to the left. An electrocardiogram was not made at the time. The sedimentation rate was strongly increased: after one hour 72 mm. and after two hours 92 mm. There was slight leukocytosis (9,800 leukocytes). On the roentgenogram rests of old specific deviations were seen. The temperature soon became normal and the pain disappeared. Tubercle bacilli were never found in the sputum, but a diagnosis of pleuritis sicca and pulmonary tuberculosis was made. The patient was discharged in fairly good condition, but after five weeks he was readmitted to the clinic. He no longer coughed, but the shortness of breath had become more pronounced. A few days prior to his readmission to the clinic he had had another attack of pain, in the right side this time, and he had coughed up some bloody sputum. Examination showed that dyspnea was marked and that both legs were edematous. The respiratory rate was 40 per minute, the pulse rate 120 and the temperature 38.6 C (101 F.). The percussion sound was dull at the base of the right lung, and on auscultation crepitant râles were heard. Again a diagnosis of pulmonary tuberculosis was made, and the patient was discharged. On Dec. 7, 1933, he was readmitted to the clinic because of general cardiac failure. At that time an electrocardiogram showed a C 1 type of tracing in lead IV and the previously mentioned characteristic changes in the standard leads. In our opinion the history of the case should be interpreted as follows: On his first admission to the clinic the patient had coronary thrombosis (with pleuropericarditis), on his second admission infarction of the lungs and on the third admission cardiac failure caused by myodegeneration. This case clearly shows the value of the chest lead in studying acute intrathoracic processes.

Case 8 (table 2, case 3; fig. 5 *C*).—A patient with an aortic aneurysm and syphilitic aortic regurgitation had had attacks of oppression for six years. There was progressive failure of the heart. An electrocardiogram showed changes of the C 1 type of tracing, probably caused by coronary stenosis due to syphilis of the aorta. As there was no acute moment recorded in the anamnesis, acute coronary obstruction probably had not occurred.

Case 9 (table 2, case 4; fig. 5 *D* and *E*).—This man aged 69 had a sudden violent sense of oppression in the cardiac region but no pain. After that he grew short of breath, and cardiac failure arose. On examination the heart appeared to be dilated to the left and to the right. There was a systolic murmur at the apex. The pulse rate was 70, the respiratory rate 26 and the temperature normal. The blood pressure was 120 systolic and 85 diastolic. The liver was palpable. There was slight jaundice. An electrocardiogram showed the typical changes of the C 1 type of tracing in all leads. In lead III no Pardee Q wave was visible, but there was a small W-shaped ventricular complex, similar to that seen in anterior infarction in lead I. The anamnesis and the electrocardiogram established the probable diagnosis of coronary thrombosis.

Case 10 (table 2, case 5; fig. 6 *A* to *C*).—Since November 1933 a woman aged 70 had repeatedly been admitted to the hospital. The diagnosis was arteriosclerotic myodegeneration with severe cardiac failure. Angina pectoris occurred at the least exertion. The heart was enormously dilated to the left and to the right, and there was congestion of the lungs. The blood pressure was 210 systolic and 105 diastolic. During the observation the electrocardiogram showed a picture which became gradually clearer and which showed in the standard leads more and more definitely the deviations of posterior infarction. Also there were changes in the chest lead, in which a C 1 type of tracing was obtained showing a small ventricular

complex. In our opinion the myocardial infarction arose, without any acute stage, from the gradually increasing coronary sclerosis, in which the posterior branch of the coronary artery was chiefly involved (lead IV was taken with the electrodes changed).

CASE 11 (table 2, case 7; fig. 6 *D*).—A girl aged 19 years was admitted to the hospital because of dyspnea. A few years before she had suffered from a second

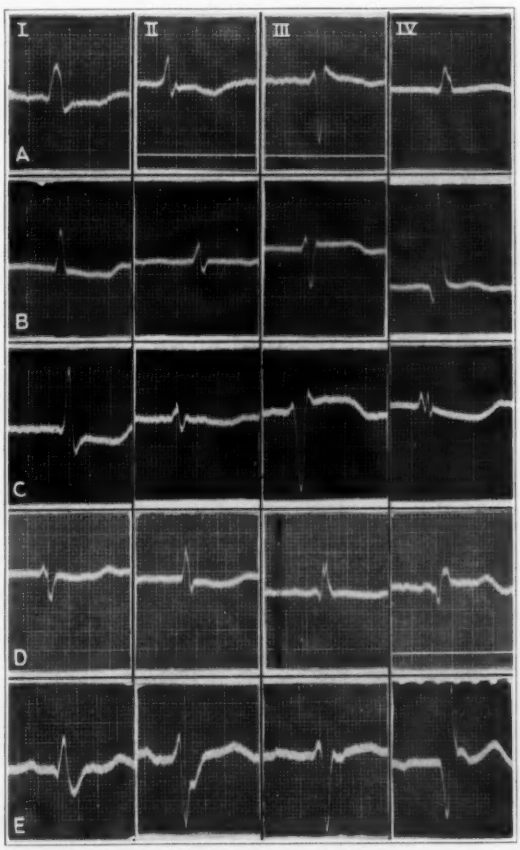

Fig. 6.—Examples of the C 1 type of tracing. For data on *A* to *C* see case 10 (section 1) and table 2, case 5. *A* was taken on Nov. 17, 1933, *B* on Oct. 3, 1934, and *C* on Sept. 3, 1935 (the electrodes were in the precordium and on the left leg). For data on *D* see case 11 (section 1) and table 2, case 7, and for *E* see table 2, case 6.

attack of acute articular rheumatism (the first attack had occurred five years previously). Examination revealed enlargement of the heart, with dilatation to the left and to the right, of the mitral type. The liver was enlarged and had a blunt

margin. Slight edema was present. The patient's condition rapidly became worse (for a few days before her admission to the clinic pericardial friction had been audible), and about two months later she died. At autopsy 200 cc. of fluid was present in the pericardium. There was fresh endocarditis of the mitral valve, and many rheumatic nodes were spread over the myocardium. It is well known that in rheumatic myocarditis the electrocardiographic picture in the standard leads may be reminiscent of coronary thrombosis, as demonstrated in this case by the chest lead.

2. ABNORMALLY DEEP T WAVES

While taking thoracic electrocardiograms with the anteroposterior or anterior-left leg lead (in which normally the T wave is negative) we sometimes saw remarkably deep T waves, and it seemed important to ascertain the clinical significance of this deviation. Master [4b] reported the following values for the T wave in normal subjects: average, —3.3 mm.; minimum, —1.5 mm., and maximum, —7.5 mm. Bohning and Katz [4e] found —5.7, —2 and —10 mm., respectively; and Goldbloom [4d] found —4.9, —2 and —8 mm., respectively. The maximum values reported by Bohning and Katz (—10 mm. in twenty-five cases) were highest, and those reported by Master (—7.5 mm. in one hundred and four graphs) were lowest. We too found in some cases —10 mm. as a maximum depth for the T wave in a normal subject; nevertheless, such a value is exceptional. In the next paragraphs T waves deeper than 10 mm. in the chest lead will be discussed.

Bohning and Katz found in 12 per cent of their curves for patients with a suspected or distinctly insufficient coronary circulation a T wave of from —8 to —11 mm. Wolferth and Wood,[2f] who sometimes found a high T wave in the chest lead in cases of anterior infarction, expected to find a very deep T wave in cases of posterior infarction. However, they have not described such a case as yet, and their supposition does not seem probable to us (see section 1). As far as we have been able to see, no attention has been paid to an abnormally deep T wave in association with other conditions. It has been pointed out by some investigators that the position of the anterior electrode influences the size of the T wave (Hoffman and Delong [12] and Roth [13]). For patients suffering from cardiac disease a deep T wave should be of significance only when the anterior electrode is in a certain position. According to these investigators the T wave increases in depth as the anterior electrode is applied nearer to the sternum, and according to Katz and others this happens when the exploring electrode is applied nearer to the cardiac apex. We also observed this in a series of electrocardiograms of normal subjects (generally the T wave increases in depth

12. Hoffman, A. M., and Delong, E.: Standardization of Chest Leads and Their Value in Coronary Thrombosis and Myocardial Damage, Arch. Int. Med. **51**:947 (June) 1933.

13. Roth, I. R.: Am. Heart J. **10**:798, 1935.

from the first intercostal space, where it is still positive, as a rule, to lower down; and the same occurs when the exploring electrode is moved from left to right in one intercostal space). Nevertheless, we found that those variations never reach values exceeding 10 mm., so that great importance may be attached to a T wave deeper than 10 mm.

Another question is how far changes of the anatomic axis of the heart influence the thoracic electrocardiogram.[5b] Einthoven and his co-workers [14] and later Cohn and Raisbeck [15] demonstrated that inversion of the T wave may be brought about by changing the angle between the horizontal and the anatomic axis. One can imagine that such a mechanism played a part in our cases in which there were abnormally deep T waves. But on measuring the previously mentioned angle (on the roentgenograms of nearly all patients) we could not find any conformity between the anatomic axis and the changes in the T wave. Then there remains the possibility that a deep T wave may be caused by a revolving of the heart on its anatomic or horizontal axis. In opposition to this theory may be stressed that fact that *various* valvular defects (stenosis or insufficiency of the aorta or of the mitral valves) are attended with such a deep T wave.

However that may be, it is of greater importance that we found organic cardiac or cardiovascular disease in forty of our forty-seven patients (85 per cent) with T waves deeper than 10 mm. This immediately draws attention to the clinical importance of an abnormally deep T wave in the chest lead. In three other patients the presence of disease was dubious (cases 3 to 5), and in four others no clear deviation of the heart could be corroborated. It is striking that the abnormally deep T wave occurred in forty-three males, whereas our electrocardiographic material represented a few more females than males. About 70 per cent of these patients were over 40 years old. Bohning and Katz attributed the deep T wave to the symptoms of coronary sclerosis. As this deviation of the coronary vessels occurs frequently, it is difficult to say whether electrocardiographic deviations like these must be ascribed to coronary sclerosis or to other additional causes. Moreover, the standard leads in our cases did not show the characteristics of coronary sclerosis. Over and above that, in many cases of electrocardiographically typical coronary sclerosis we saw no deep T waves in the chest leads.[15a] Nevertheless, we cannot deny the possibility that coronary deviations play a part in the causation of deep

14. Einthoven: Arch. internat. de physiol. **4**:132, 1906; Arch. f. d. ges. Physiol. **122**:517, 1908.

15. Cohn, A. E., and Raisbeck, M. J.: Heart **9**:311 and 331, 1922.

15a. An article about changes due to coronary sclerosis will be published by us later.

T waves; one can presume that in cases of hypertension, chronic nephritis, defects of the aortic valves and arteriosclerotic myodegeneration the coronary vessels are not without defects. On the other hand, this explanation is less probable in cases of mitral stenosis (with usually a low tension), mitral insufficiency and exophthalmic goiter.

TABLE 3.—*Data on the T Waves in Leads I to IV*

Sex	Age	Diagnosis	Blood Pressure, Mm. of Mercury	T_1, Mm.	T_2, Mm.	T_3, Mm.	T_4, Mm.
M	47	Essential hypertension	260/180	—3	—2	1	—11
M	49	Essential hypertension	165/100	3	3	—1	—16
M	62	Essential hypertension	195/100	diph. 1	—2	—1	— 9
M	67	Essential hypertension	220/110	0	0	0	—16
F	61	Hypertension	175/100	—1	diph. 2	3	—13
F	57	Hypertension	200/100	0	1	2	—13
M	58	Hypertension (case 2, section 2)	250/130	2	2	2	—28
M	72	Hypertension	210/110	1	1	0	—18
M	65	Hypertension	235/110	1	1	0	—10
M	62	Hypertension	275/140	2	2	1	—13
M	54	Hypertension; Bright's disease	200/120	diph. 2	diph. 1	3	—16
M	54	Aortic stenosis	150/ 90	—5	—3	2	—22
M	15	Aortic and mitral regurgitation	155/ 0	—5	diph. 2	5	—12
M	47	Aortic regurgitation	170/ 0	0	—3	—2	—15
M	46	Aortic regurgitation	134/ 58	diph. 1	diph. 1	0	—15
M	65	Aortic regurgitation	235/110	1	1	0	—10
M	51	Aortic regurgitation and stenosis	180/ 70	2	3	1	—11
M	41	Mitral insufficiency	175/110	—2	diph. 1	2	—15
M	58	Mitral insufficiency	135/ 90	5	5	—1	—20
M	64	Mitral insufficiency	145/ 90	—2	3	7	—13
M	34	Mitral insufficiency	125/ 80	4	9	5	—18
M	33	Mitral stenosis	110/ 60	6	7	4	—18
M	55	Mitral stenosis	130/ 70	3	5	2	—12
M	33	Mitral stenosis	125/ 70	4	5	3	—15
M	37	Mitral stenosis	110/ 85	4	5	1	—10
M	21	Mitral insufficiency (case 1, section 2)	120/ 45	0	9	10	—30
M	56	Mitral insufficiency	115/ 70	1	0	0	—12
M	61	Complete heart block	195/ 70	diph. 2	6	6	—18
F	64	Bundle branch block	175/100	—7	2	8	—16
M	54	Bundle branch block	150/ 90	—5	—3	2	—22
M	57	Arborization block	155/100	0	0	2	—13
F	66	Myodegeneration	120/ 55	—2	—2	0	—18
M	52	Myodegeneration	110/ 65	4	3	—1	—12
M	60	Myodegeneration	135/ 75	2	3	3	—12
M	58	Myocarditis	135/ 75	diph. 2	4	5	—10
M	65	Coronary sclerosis	140/100	—3	0	3	—13
M	56	Angina pectoris	135/ 90	4	4	1	—14
M	52	Auricular fibrillation	140/ 85	4	0	1	—11
M	72	Auricular fibrillation	130/ 75	1	1	0	—12
M	27	Rheumatic polyarthritis	130/ 85	7	5	diph. 1	—15
F	28	Exophthalmic goiter	150/ 0	4	4	2	—13
M	43	No deviations	130/ 65	4	7	5	—13
F	49	Case 4	125/ 75	2	5	2	—14
M	33	Case 3	120/ 75	6	7	2	—14
M	26	Case 5	135/ 85	4	6	4	—13
M	31	No deviations	130/ 80	1	4	3	—13
M	39	No deviations	130/ 70	3	5	3	—15

As a working hypothesis we may assume that in cases of mitral defects revolving of the heart and in some other cases coronary changes play a part. The deep T waves were partly found in bundle branch or arborization block, in analogy to the diphasic ventricular complexes in the other leads (fig. *7 D*). As for the T waves in the other leads (table 3): in twenty-seven cases the T waves in leads I and II were positive (though low in seven), and in the other twenty cases in both lead I and II the T wave was either negative or flat. Positive T waves in the three standard leads were found seventeen times in forty-seven

cases; so in more than one third of all cases lead IV offered the only deviation! This demonstrates the importance of the chest lead for this group as well as for the others. It impressed us that in the four cases of mitral stenosis in which there were deep T waves the T waves in the limb leads were always positive. Now the question arises as to how far this T wave indicates insufficiency of the myocardium. In about one third of the cases there were clinical indications of decompensation (dyspnea, cyanosis, a distinctly more rapid pulse rate, edema and congestion of the lungs); in the other cases these symptoms were absent.

In summarizing our data we may say that the greater part of our patients (85 per cent) who showed a deep T wave in the thoracic electrocardiogram clearly showed signs of organic disease of the heart or of the cardiovascular system; in some cases such diagnoses were plausible, though they could not be proved (5 per cent), and in the other cases (10 per cent) they could not be demonstrated. The deep T wave did not prove to be a sure sign of myocardial insufficiency. The following case reports illustrate these features.

CASE 1 (fig. 7 *A*).—A man aged 21 was suffering from a combined mitral defect. He complained of palpitations, shortness of breath and a heavy feeling in the cardiac region on exertion. These symptoms began six years before his admission to the clinic, after an attack of acute polyarticular rheumatism. On examination a raising impulse was found which extended outside the medioclavicular line; on percussion the heart appeared to be enlarged to the left and to the right, and on auscultation a loud first sound and a soft presystolic and a rough systolic murmur were heard. An electrocardiogram [9] showed a large ventricular complex in the first lead, right axis deviation and high T waves in leads II and III. In lead IV the T wave was 30 mm. deep.

CASE 2 (fig. 7 *B*).—A man aged 58 had a blood pressure of 250 systolic and 130 diastolic. The heart was slightly enlarged to the left, with a somewhat widened aorta. For the rest there were no clear deviations. The diagnosis was arteriosclerotic hypertension and arteriosclerosis of the aorta. An electrocardiogram showed strong left axis deviation. In leads I to III the T wave was low, but in lead IV it was 28 mm. deep.

CASE 3 (fig. 7 *C*).—A man aged 33 complained of slight oppression and palpitations on exertion. On physical examination no important deviations from normal were found. The blood pressure was 120 systolic and 75 diastolic. Tests for syphilis were negative. Percussion and auscultation of the heart revealed no abnormality. However, roentgen examination showed that the aorta was wide and that the heart was dilated to the left. We therefore could not consider the heart of this patient to be entirely normal. The only peculiarity shown by the electrocardiogram was that the T wave in lead IV was 14 mm. deep.

CASE 4.—A woman aged 49 had for some time complained of attacks of palpitation, which occurred about once a fortnight. After such an attack the patient vomited and urinated several times. She was greatly fatigued. On physical examination no deviations were found, except that once there was total irregular tachycardia. Such an attack was not recorded electrocardiographically. The only

peculiarity the electrocardiogram showed was a T wave of —14 mm. in lead IV. It is not improbable that this woman suffered from paroxysmal auricular fibrillation. Therefore, it is possible, though it cannot be proved, that the depth of T_4 here implied a pathologic condition.

Case 5.—A man aged 26 complained of having sometimes a gripping feeling in the chest, together with vomiting. This had nothing to do with exertion, eating or emotion. Otherwise the patient was in good health. The blood pressure was normal. The heart showed no peculiarities either on the roentgenogram or on

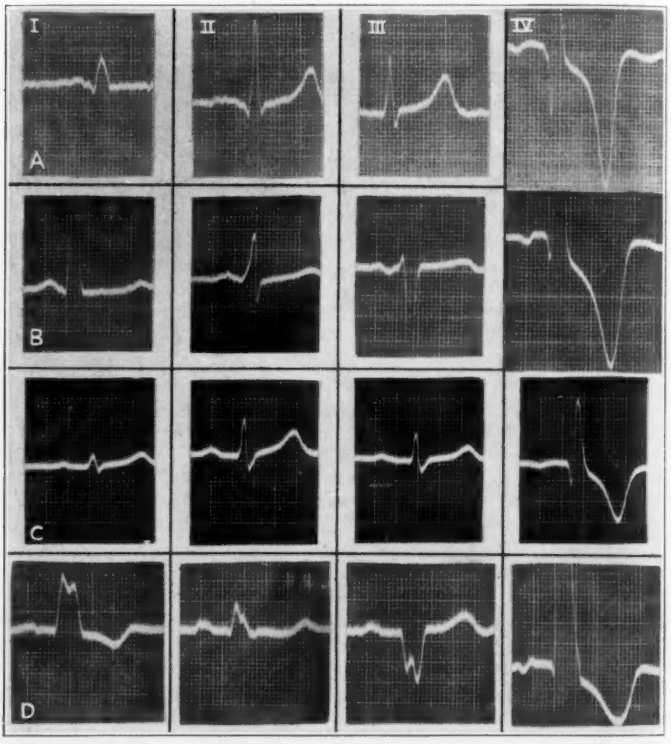

Fig. 7.—Examples of deep T waves. *A* (case 1, section 2) shows a deep T wave in mitral stenosis. *B* (case 2, section 2) shows a deep T wave in arteriosclerotic hypertension. For data on *C* see case 3, section 2. *D* shows a deep, broad T wave in bundle branch block.

physical examination. The urine contained some albumin, erythrocytes and granular casts. The only peculiarity the electrocardiogram showed was a T wave of —13 mm. in lead IV. Does such an electrocardiographic picture offer the starting point for making a diagnosis of disease of the heart? For the present we do not believe that it does.

3. THE FLAT AND INVERTED T WAVE

Not only in cases of myocardial infarction due to coronary thrombosis but also in cases of damage to the myocardium due to other causes the chest lead may be of diagnostic value. Wood and Wolferth and their co-workers [2c] have already pointed this out. Hoffman and Delong [12] were the first to study the deviations of the T wave in lead IV in some cases of myodegeneration and other diseases of the myocardium. However, they came to the conclusion that the standard leads as a

TABLE 4.—*Data on the T Waves in Leads III and IV*

Sex	Age	Diagnosis	T_3	T_4
F	52	Hypertension; diabetes	—	+
M	66	Hypertension; diabetes	—	+
F	52	Hypertension; angina pectoris	—	Trace
F	55	Hypertension	—	+
F	36	Hypertension	—	Shallow
F	61	Hypertension; angina pectoris	—	+
F	61	Hypertension	—	Shallow
F	41	Hypertension	Trace	Shallow
F	40	Hypertension (hypernephroma ?)	—	Shallow
F	44	Hypertension	Trace	Trace
F	50	Hypertension	—	+
F	44	Hypertension	—	Diphasic
F	40	Hypertension	Flat	Flat
F	9	Hypertension	—	Flat
F	47	Angina pectoris	+	+
F	36	Angina pectoris	—	+
F	44	Angina pectoris	—	Diphasic
F	46	Angina pectoris	—	+
F	35	Anginous syndrome	Diphasic	Diphasic
F	45	Coronary sclerosis	—	—
F	45	Coronary sclerosis; diabetes	—	Flat
F	50	Myodegeneration	Flat	+
F	36	Heart failure	—	Shallow
F	30	Aortic regurgitation	—	Diphasic
F	53	Syphilitic aortitis	Flat	Shallow
F	41	Mitral stenosis	Diphasic	Diphasic
F	22	Auricular extrasystoles	Flat	+
F	36	Extrasystoles; heart failure	Flat	Shallow
M	7	Ventricular extrasystoles	Diphasic	Shallow
F	20	Ventricular extrasystoles	—	Shallow
F	14	Ventricular extrasystoles	—	Diphasic
F	9	Ventricular extrasystoles	Diphasic	+
F	41	Exophthalmic goiter	—	+
F	39	Exophthalmic goiter	—	Shallow
F	35	Simple goiter	—	Shallow
F	16	Simple goiter; tachycardia	Diphasic	Shallow
M	5	Diphtheria; nephrosis	Diphasic	+
F	7	Diphtheria	—	Diphasic

rule offer sufficient data about the condition of the myocardium. Bohning and Katz [4b] favored the same opinion, and of late Scherf [14] has once more defended this view. Korth and Hecht,[16] on the other hand, published examples which illustrated the importance of the chest lead in diffuse myocardial lesions, when the limb leads answer this question either insufficiently or not at all. One of us (van Nieuwenhuizen [4a]) described some cases of rheumatic myocarditis in which plain deviations were seen only in lead IV, whereas in some cases the picture of the T wave in the fourth lead changed analogically with the condition of the patient.

16. Korth, C., and Hecht, H.: Klin. Wchnschr. **14**:992, 1935.

In our first group of fifteen hundred electrocardiograms with four leads we found deviations of the T wave in the chest lead (except those mentioned in sections 1 and 2) in one hundred and fifty-five cases. In forty-six of them the T wave in leads I and II was either low or flat or negative. As the chest leads in this group did not settle the diagnosis, these cases will be left out of consideration. Forty-four of the other one hundred and nine electrocardiograms showed a flat, low or negative T wave in the third lead (table 4). In this group the chest lead (with a restriction to be mentioned later) as a rule settled the question of judging the condition of the myocardium. In the remaining sixty-five electrocardiograms only the fourth lead deviated from the standard (table 5). These figures show that the chest lead does not correspond exactly with the standard leads. The desirability of bringing the electrocardiographic method to perfection when diagnosing diffuse myocardial damages will be appreciated by every one who is familiar with those frequent cases in which there are obvious clinical symptoms of cardiac failure but the limb leads do not show typical changes. However, when the T wave in the fourth lead is being judged some factors must be considered. It is agreed that digitalis influences the shape of the T wave just as much in the chest lead as in the standard leads (Strauss;[17] van Nieuwenhuizen[4a]). Also, just as in limb leads, heating or cooling the surface of the chest above the cardiac apex may cause an inversion of the T wave (Jervell[18]). Finally, it impressed us that sometimes a positive T wave was found in the anteroposterior or the anterior left leg lead in clinically healthy subjects, especially children. On closer examination we found that these patients had a "dropping heart," or a long, steep heart, of which the low R wave in lead I and high R waves in leads II and III were mostly, but not always, the expression in the limb leads. Also as a rule the T wave was low in lead I and high in lead II. When interpreting the thoracic electrocardiogram it is important to remember this fact and not to consider an inverted T wave in lead IV in patients with long, steep hearts and in children as a symptom of myocardial disease. Recently Graybiel and White[19] described a negative T wave in the standard leads in fairly normal subjects. However, an examination of their case reports shows that some of the patients suffered from paroxysmal tachycardia and thyrotoxicosis. Aside from these less convincing cases, there were some in which a diagnosis of "neurocirculatory asthenia" had to be made. Of course it cannot be denied that a gradually intruding infection may have developed, but that would

17. Strauss, H., and Katz, L. N.: Am. Heart J. **10**:546, 1935.
18. Jervell, A.: Acta med. Scandinav., supp. 68, 1935, p. 1.
19. Graybiel, A., and White, P. D.: Am. Heart J. **10**:345, 1935.

stamp the electrocardiographic and clinical diagnoses *ad absurdum*. It must not be forgotten that Lewis found the T wave minimally to be —0.5 mm. in lead I in normal subjects, and in lead II there was sometimes a "trace." Possibly our cases of inverted T waves in

TABLE 5.—*Further Data on the T Waves in Leads III and IV*

Case	Sex	Age, Years	Diagnosis	T_3	T_4
1	F	39	Hypertension	+	Diphasic
2	F	53	Hypertension	+ +	+
3	M	75	Hypertension	+	Shallow
4	F	59	Hypertension	Flat	Flat
5	F	31	Hypertension	Flat	Shallow
6	F	61	Hypertension	+	+
7	F	45	Hypertension	Flat	Shallow
8	F	14	Hypertension; Bright's disease	+	+
9	F	56	Hypertension; diabetes	+	+
10	M	42	Hypertension; angina pectoris	+	+ High
11	F	47	Hypertension; angina pectoris	+	+
12	F	32	Angina pectoris	Diphasic	+
13	F	59	Angina pectoris	Flat	Shallow
14	F	43	Angina pectoris	Flat	Shallow
15	F	50	Coronary sclerosis	Flat	Flat
16	M	51	Coronary sclerosis; heart dilated	+	+
17	F	57	Coronary sclerosis	+	Shallow
18	F	50	Coronary sclerosis	+	Shallow
19	M	45	Coronary sclerosis; emphysema	+	Shallow
20	M	61	Coronary sclerosis; diabetes	Flat	Shallow
21	F	41	Numerous extrasystoles	+	+
22	F	1½	Numerous extrasystoles following diphtheria	+	+
23	F	36	Numerous extrasystoles; escaped beats	+	Shallow
24	M	41	Nervous tachycardia	Flat	Shallow
25	F	18	Nervous tachycardia	+	Shallow
26	F	55	Palpitations	+	Shallow
27	F	31	Paroxysmal tachycardia (?)	+	Diph.
28	F	58	Exophthalmic goiter	+	Diph.
29	F	11	Exophthalmic goiter	+	+
30	F	14	Exophthalmic goiter	Flat	Shallow
31	F	21	Exophthalmic goiter	+	Diph.
32	F	27	Exophthalmic goiter	+	+
33	F	38	Exophthalmic goiter	+	+
34	F	21	Mitral stenosis	Flat	+
35	F	48	Mitral stenosis	+	Shallow
36	F	20	Mitral stenosis	+	+
37	F	42	Mitral stenosis	+	Shallow
38	F	56	Mitral stenosis; insufficiency	Flat	+
39	F	29	Mitral insufficiency	+	Shallow
40	M	57	Mitral insufficiency	+	Diph.
41	F	24	Mitral insufficiency	+	Shallow
42	M	43	Aortic regurgitation	+	+
43	M	10	Postrheumatic complicated defect	+	+
44	M	12	Endocarditis	+	+
45	M	7	Sydenham's chorea	Flat	+
46	M	2½	Congenital malformation	+	+
47	M	15	Congenital malformation	+	Shallow
48	F	36	Aneurysm of subclavian artery	Flat	+
49	F	2	Bronchopneumonia	+	+
50	F	30	Dropping heart	Flat	Shallow
51	M	12	Dropping heart	+	+
52	F	35	Headache	+	Shallow
53	F	37	Hysteria	+	+
54	M	38	Tumor of spinal cord	+	+
55	F	19	Neurotic complaints	+	Shallow
56	M	15	Syncopes without known origin	+	Shallow
57	F	16	Pains in back	+	+
58	F	34	Cholelithiasis	+	Flat

fairly normal persons are analogous to those of White (in which the cause was not known); but to us it seems more probable that the position of the heart was the causal factor.

CASE 1 (table 5, case 33; fig. 8 *A*).—A woman aged 38 suffered from hyperthyroidism. She had distinct tremors of the hands and a pulse rate of 104. The

blood pressure was 200 systolic. The basal metabolism was +61 per cent. A roentgenogram showed the heart to be dilated to the left, possibly with dilation of the right ventricle. An electrocardiogram showed no distinct deviations in leads I and II; in lead III the T wave was low but positive in the anteroposterior lead. So here the chest lead offered the only electrocardiographic sign that this severe hyperthyrosis was combined with disease of the myocardium.

CASE 2 (table 5, case 40; fig. 8 *B*).—A workman aged 57 suffered from stomach trouble and palpitations. Sometimes he awoke with an intense pain in the cardiac region. The blood pressure was 100 systolic and 75 diastolic. There was slight peripheral arteriosclerosis. On percussion and roentgenographically the heart appeared to be enlarged. Above the mitral valve a systolic murmur was heard. The diagnosis was mitral insufficiency. The liver was slightly enlarged. An electrocardiogram showed low ventricular complexes in lead I; the course of the ST segment was aniso-electrical and saddle shaped. In lead II there were small ventricular complexes with a notch in S. In lead III the course of ST was aniso-

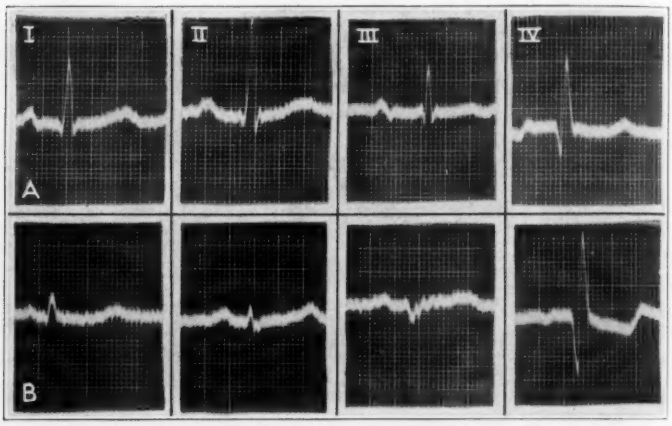

Fig 8.—Examples of diphasic and positive T waves following diffuse injury to the myocardium. For data on *A* see case 1, section 3, and for *B* see case 2, section 3.

electrical; here too the ventricular complexes were small. In all three leads the T waves were positive. In lead IV the T wave was diphasic. With the other deviations these findings indicated a none too favorable condition of the myocardium. It is a question whether here there was not a C 2 type of tracing, which then indicated the pressure of anterior infarction which had arisen chronically.

SUMMARY

Data obtained from the chest lead derived as a routine method are discussed on a basis of fifteen hundred tracings. In coronary thrombosis the chest lead often offers the only electrocardiographic diagnostic evidence. The importance of the chest lead for the differential diagnosis of acute intrathoracic or abdominal deviations with coronary

thrombosis is pointed out. The chest lead may be of much value also in reaching a diagnosis in a case of gradually arising myocardial infarction. The tracings obtained in coronary thrombosis are divided into two groups, one of which (C 2 type, fig. 1 *B* and *C*) was caused by anterior infarction and the other (C 1 type, fig. 1 *D* and *E*) possibly by posterior or septal infarction.

It is not improbable that these last curves indicated an atypical bundle branch block. But there still remains the question whether the cause is not an insufficiency of the blood supply by the posterior coronary artery.

The latter form of tracing (C 1) was seen in one case of rheumatic myocarditis. The history of a patient in the first group usually records an acute attack; that of a patient in the second group usually bears no record of a sudden attack of pain or oppression. This is the reason these myocardial changes often escape clinical observation. Next the clinical significance of an abnormally deep T wave (deeper than — 10 mm.) is pointed out. With a few exceptions such a wave is always found in organic disease of the heart. In cases of mitral stenosis, however, the T waves in the standard leads are strongly positive; in other groups (hypertension, chronic nephritis and aortic defects) all or part of them are abnormal. The hypothesis is advanced that the deep T wave in mitral stenosis is the result of a difference in the position of the heart; in the other groups this might be the result of myocardial disease. A deep T wave is found also in bundle branch block. Then, however, the ventricular complex is very high and large, in analogy to the diphasic ventricular complexes in the other leads.

Finally the importance of the chest lead in making an electrocardiographic diagnosis of diffuse myocardial damage is demonstrated either as a support for the third lead (table 4) or as the sole criterion (table 5). Here the T wave may be shallow, diphasic or positive. Other factors which influence the shape of the T wave in the chest lead are digitalis and a longitudinal position of the heart, especially in children.

ANATOMIC FEATURES OF THE CARDIAC ORIFICE OF THE STOMACH

WITH SPECIAL REFERENCE TO CARDIOSPASM

FREDERICK C. LENDRUM,* M.D., PH.D.
DETROIT

The clinical problems which concern the lower end of the esophagus and the cardiac orifice of the stomach are basically anatomic problems. The occurrence and nature of esophageal varices depend on the venous supply and the anastomoses across the cardia, as has been demonstrated by Kegaries.[1] The study of peptic ulcer of the esophagus raises the question of the competence of the sphincteric action of the cardia in preventing the regurgitation of gastric juice and also the question of the occurrence of islands of gastric mucosa in the esophagus. Carcinoma of the cardia and the lower extremity of the esophagus also is of extreme anatomic interest. The peculiar glandular epithelium which is present at the cardia might be expected to give rise to neoplasms which have different properties from those of neoplasms which originate elsewhere in the stomach and esophagus. Moreover, the metastasis of a carcinoma at the cardia depends on the distribution of the lymphatic glands in this region, which has been much less satisfactorily studied than has the lymphatic drainage of the stomach. Finally, the phenomenon of cardiospasm, which is the most important clinical condition associated with this region, doubtless depends for its explanation on some peculiarity of the musculature, nerve supply or external pressure at this point in the enteric canal.

Much labor has been spent on the study of the anatomic features of the stomach, and no small amount of attention has been directed also to the esophagus. Surprisingly little thought, however, has been given to the point of transition between these two organs. Accordingly, for the most part there are no adequate descriptions of what happens to the various tissues as they pass from the esophagus into the stomach. For the purposes of the present paper the word cardia will be used to cover this region of transition, including the lower extremity of the esophagus,

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1. Kegaries, D. L.: The Venous Plexus of the Esophagus: Its Pathological and Clinical Significance, Thesis, University of Minnesota Medical School, 1932.

the point of juncture with the stomach and the adjacent portions of the stomach. If the term cardia should sound to the literary purist like a colloquial modern abbreviation for "cardiac orifice," it may console him to know that this word was used in the "Commentaries" of Heberden [2] as early as 1802.

GENERAL DESCRIPTION OF THE CARDIAC ORIFICE

After passing through the diaphragm the lower end of the esophagus curves to the left and enters the inner aspect of the upper end of the stomach at the cardiac orifice. In the human adult the abdominal portion of the esophagus, which is termed the cardiac antrum, is about 2 cm. in length. At the cardiac orifice the right margin of the esophagus is continuous with the lesser curvature of the stomach, while the left margin joins the greater curvature at an acute angle, which is termed the incisura cardiaca. This angulation is dependent on the form and position of the adjoining fundus.

When the esophagus and stomach are opened at necropsy, the mucous membrane at the cardia presents an abrupt change in appearance from the smooth, white, opaque, parchment-like mucous membrane of the esophagus and the mamillated pink mucus-covered lining of the stomach. This contrast more often than not is partially effaced by postmortem erosion around the cardia.

The esophageal epithelium terminates not in a straight but in a jagged, irregular and angulated line. Just below this line in the adult there is a groove, which is formed by the orifices of the cardiac glands, which in the adult undermine the lower end of the esophageal epithelium. Microscopically the epithelium of the esophagus is observed to be, in the human species, of a thick noncornified stratified squamous variety, with numerous papillae, arranged linearly in the axis of the esophagus (fig. 1). At the cardia the stratified squamous epithelium of the esophagus changes abruptly to the simple columnar epithelium of the stomach (fig. 2). Beneath both varieties of epithelium, at intervals of about 2 or 3 mm. in the ordinary section, are the mucosal lymph follicles. Likewise, beneath both varieties of epithelium are the cardiac glands. In the human infant, as well as in eight other species of mammals which I have examined, the cardiac glands have the structure of stunted or incomplete fundic glands. Bensley,[3] who has

2. Heberden, William: Commentaries on the History and Cure of Diseases, London, T. Payne, 1802.

3. Bensley, R. R.: The Cardiac Glands of Mammals, Am. J. Anat. **2**:105-156 (Nov. 29) 1902; The Cardiac Glands of the Mammalian Stomach, Anat. Rec. **4**: 375-390, 1910; The Gastric Glands, in Cowdry, E. V.: Special Cytology: The Form and Function of the Cell in Health and Disease, New York, Paul B. Hoeber, Inc., 1928, vol. 1, pp. 139-167.

investigated the cardiac glands in much detail, concluded that they are essentially fundic glands the development of which has been in some way inhibited. This inhibitory influence is apparently lost in middle adult life, when the cardiac glands undergo an adenomatous hyperplasia which produces bizarre irregular masses of glandular tissue.

The cardia is the site of striking changes in the subepithelial connective tissue, which take place by gradations over the region occupied by the cardiac glands. In the esophagus there is a fairly thick layer of connective tissue and lymph follicles between the epithelium and the muscularis mucosae. This layer is more cellular and much more dense than the submucosal layer, which it approaches in thickness. It con-

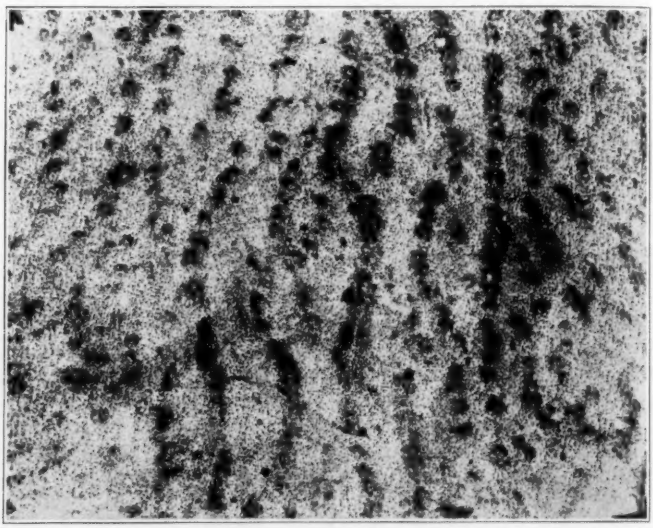

Fig. 1.—Full thickness section of the esophageal mucosa at the cardia, cleared to show the linear longitudinal arrangement of the papillae (× 28).

tains no fat cells. The lamina of subepithelial connective tissue continues unchanged to the lower border of the esophageal epithelium. In the region of the cardiac glands this layer is invaded and distorted by irregular masses of glandular tissue. When the true fundic glands are reached, the muscularis mucosae is applied directly to the fundic ends of the glands, and the mucosal layer of connective tissue almost disappears.

No less dramatic are the changes which take place in the muscularis mucosae. Throughout the esophagus the muscularis mucosae is very thick; in fact, it is possible to find sections in which it equals in thick-

ness that of the outer longitudinal layer of the muscularis propria. The muscularis mucosae has no sheath. It does not form even a single dense lamina but is made up of ragged longitudinal strands of smooth muscle separated by connective tissue. In the small intestine the muscularis mucosae is made up of an inner circular and an outer longitudinal layer. In the larger part of the stomach it is made up of three layers. However, in the esophagus, at the cardia and in the neighboring few centimeters of the stomach I have never seen anything except longitudinal fibers in the muscularis mucosae. The muscularis is unchanged throughout the esophagus as far as the cardia. The cardiac glands in

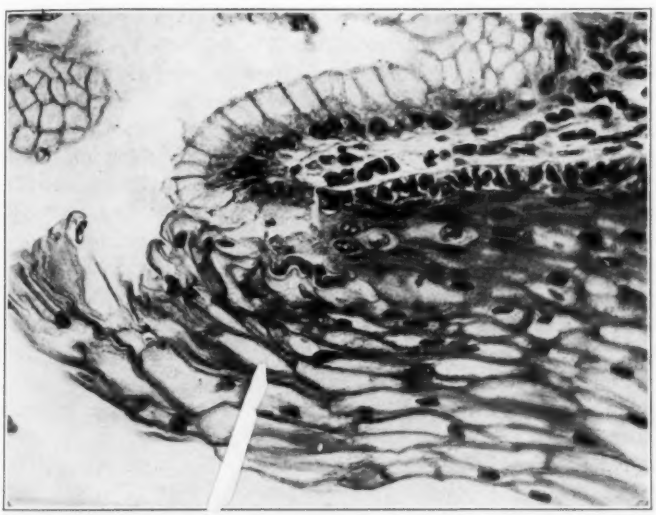

Fig. 2.—Point of juncture between the squamous and the columnar epithelium at the cardia (× 340).

the adult sometimes break into the muscularis, so that while these glands lie mostly superficial to the muscularis, strands of muscular tissue may surround the deep layers of the cardiac glands. As soon as the muscularis mucosae reaches the region of the fundic glands, which is generally within 1 or 2 cm. of the end of the esophageal epithelium, it becomes a much thinner but more dense and regular layer and is applied closely to the ends of the glands.

The submucous layer of the esophagus is composed of acellular loose connective tissue. The submucosal layer contains the esophageal glands proper, which are closely applied to the outer surface of the muscularis mucosae. It contains also a few scattered fat cells. As the submucous layer passes down the esophagus and into the stomach, it

gradually becomes more dense, but there is no sudden change or break at the cardia. The submucosa contains many more and larger vessels than are present in the mucosa. It contains also Meissner's submucous plexus, the strands of which are sparse and greatly attenuated in the region of the cardia and are difficult to demonstrate. I have never seen ganglion cells in the submucous plexus of the human esophagus. Greving [4] also failed to find them, and Koslowski [5] apparently demonstrated that they do not occur in the submucous plexus of the esophagus of the cat or rabbit.

External to the submucosa is the circular muscle, arranged in bundles, with an inner and an outer sheath of connective tissue. Outside this lies the intermuscular septum, which contains the myenteric (Auerbach) plexus, in addition to a network of blood vessels. In the esophagus the intermuscular septum is a thick layer of connective tissue, and the same is true for the cardia. In the middle of the lesser curvature of the stomach, however, the intermuscular septum is greatly thinned; and when the small intestine is reached, there is no longer any intermuscular septum, and the ganglions of the myenteric plexus lie naked between the two muscular layers.

External to the intermuscular septum lies the longitudinal muscle. This muscle is ordinarily about half the thickness of the circular muscle and like it is arranged in bundles. These bundles are densely packed in the adult, but in the new-born infant the bundles may be sufficiently separated so that single longitudinal sections may give the impression of "breaks" in the longitudinal muscle. In the stomach below the cardia the layer of longitudinal muscle gradually becomes thinner.

In the human being the muscle at the cardia is all smooth muscle. Though occasional instances have been described in which striated muscle fibers have extended down this far (as by Arey and Tremaine [6]), I have never seen anything but smooth muscle in the region of the cardia. In the adventitia, of course, strands of striated muscle, which extend from the diaphragm, are frequently present.

The adventitia in the region of the cardia contains much loose acellular connective tissue, with coarse longitudinal elastic fibers and large nerve trunks. The larger blood and lymph vessels course in this layer.

MUSCULARIS PROPRIA

Because of the vast practical importance of the clinical phenomenon of cardiospasm, the anatomic aspect of the cardia which arouses most

4. Greving, R., quoted by Kuntz.[34]

5. Koslowski, quoted by Kuntz.[34]

6. Arey, L. B., and Tremaine, M. J.: The Muscle Content of the Lower Esophagus of Man, Anat. Rec. **56**:315-320 (July 25) 1933.

general interest is the question of a sphincter muscle in this situation; for it is by no means established that the condition which may be termed idiopathic dilatation of the esophagus is actually the result of spasm at the cardia. Spasm of the diaphragm, pressure by the liver, pressure by the "tips" of the lungs, paralysis of the esophagus, failure of the reflex relaxation of the cardia, fibrosis of the terminal portion of the esophagus and torsion of the esophagus are other causes which are used to explain this malady. Even the site of obstruction in cardiospasm is not agreed on. Carman [7] said that it is generally at the diaphragmatic orifice, while Alvarez asserted that it is 2 cm. lower, at the cardia.

Some enlightenment on this confusion of theories might be expected if a satisfactory answer could be obtained to the question whether or not the cardia has a sphincter to "go into spasm." This might seem to be the simplest of straightforward anatomic problems, but the investigators are hopelessly at odds about it. Hurst,[8] Thieding,[9] Schreiber,[10] Bennett,[11] Cannon [12] and Todd [13] asserted that there is an anatomic sphincter at the cardia. Zaaijer,[14] Fleiner,[15] Jackson [16] and Plenk [17] denied the existence of such a sphincter. Abel [18] asserted that there is a sphincter but said that the sphincter is not at the cardia but 1 inch above, at the diaphragmatic orifice. Mosher at one time asserted that the sphincter is "a definite and satisfying structure" and at a later date stated that it does not exist; and this *sic et non* could be continued almost indefinitely.

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7. Carman, R. D.: The Roentgen Diagnosis of Diseases of the Alimentary Canal, ed. 2, Philadelphia, W. B. Saunders Company, 1920.

8. Hurst, A. F.: Les sphincters du canal alimentaire et leur signification clinique, Arch. d. mal. de l'app. digestif **15**:1-34 (Jan.) 1925.

9. Thieding, Friedrich: Ueber Cardiospasmus, Atonie und "idiopathische" Dilatation der Speiseröhre, Beitr. z. klin. Chir. **121**:237-300, 1921.

10. Schreiber, quoted by Sturtevant.[44]

11. Bennett, T. I.: The Stomach and Upper Alimentary Canal in Health and Disease, London, William Heinemann, 1925.

12. Cannon, W. B.: The Mechanical Factors of Digestion, London, Edward Arnold & Co., 1911.

13. Todd, T. W.: The Clinical Anatomy of the Gastro-Intestinal Tract, London, Longmans, Green & Co., 1915.

14. Zaaijer, J. H.: Cardiospasm in the Aged, Ann. Surg. **77**:615-617 (May) 1923.

15. Fleiner, W.: Neue Beiträge zur Pathologie der Speiseröhre, München. med. Wchnschr. **47**:529-531 (April 17) 1900.

16. Jackson, Chevalier: Bronchoscopy and Esophagoscopy, ed. 2, Philadelphia, W. B. Saunders Company, 1927.

17. Plenk, H.: Der Magen, in Möllendorff, Wilhelm: Handbuch der mikroskopischen Anatomie des Menschen, Berlin, Julius Springer, 1927, vol. 5, pt. 2, pp. 1-234.

18. Abel, A. L.: Oesophageal Obstruction: Its Pathology, Diagnosis and Treatment, London, Humphrey Mulford, 1929.

On analysis, however, this conflict of opinion is not as disturbing as might be expected. The proponents of the sphincter in general (Abel,[18] Mosher,[19] and Hurst, for example) did not attempt to defend their opinions with minute dissections or serial reconstructions. They were content to present the photographs of one or two specimens of stomach and esophagus which showed a puckering and muscular thickening at the point of juncture. Abel,[18] in particular, said that the sphincter can be satisfactorily demonstrated only by the injection of from 6 to 8 quarts (6 to 8 liters) of solution of formaldehyde into the arteries immediately after death. The error of this method will be apparent at once to any one familiar with the appearance of embalmed organs. In subjects embalmed soon after death there frequently are rings of constriction and muscular thickening every few feet along the whole length of the gastro-intestinal tract. According to the anatomic technic under consideration, the points at which the intestine was fixed in a state of contraction must all be interpreted as sphincters.

The question of a physiologic sphincter at the cardia is not of concern here. There are three morphologic details, however, which may be expected if an anatomic sphincter exists at the cardia: first, a distinct band of circular muscle marked off from the adjoining muscle by connective tissue septums; second, an associated dilator muscle formed by the dipping into the circular muscle of longitudinal fibers, and, third, a local thickening of the circular muscle which persists after the factor of local spasm has been eliminated.

More than one hundred and fifty human cardias were examined microscopically with multiple sections and stains. These specimens covered the whole range from fetal life to advanced senility. In none of the specimens was there seen any special band of circular muscle separated by partitions of connective tissue. In contrast to what Horton observed at the pylorus, both circular and longitudinal muscles appear to be absolutely continuous from the esophagus into the stomach. The circular muscular fibers, it is true, are arranged in anastomosing bundles with connective tissue septums, which is the usual structure in the human gastro-intestinal canal. No septum at the cardia, however, is any larger or more clearly defined than are the others.

Dilator muscles are so generally seen in association with sphincters that the presence of a dilator muscle may be regarded as evidence in favor of the existence of a sphincter. At the pylorus, for example, as Horton [20] and others have demonstrated, many of the longitudinal fibers

19. Mosher, H. P.: The Lower End of the Oesophagus at Birth and in the Adult, J. Laryng. & Otol. **45**:161-180 (March) 1930.

20. Horton, B. T.: Pyloric Musculature with Special Reference to the Pyloric Block, Thesis, University of Minnesota Medical School, 1928.

dip in and become buried in the circular muscle to form a dilator of the pyloric canal. In none of the specimens examined was this observed at the cardia. It must be mentioned, however, that in many fetal cardias small isolated strands of smooth muscle from the longitudinal layer were observed to curve in and to be inserted on the connective tissue septum of the inner circular layer. Serial sections revealed that these microscopic pictures represented only aberrant filaments and were not part of a cuff of dilator fibers which extends around the cardia.

In general, the cardias which I examined at necropsy did not reveal any localized muscular thickening. Occasionally, however, particularly in embalmed specimens, the cardia was observed to be puckered and in a state of contraction, and a diffuse ring of thickened muscle was noted at the orifice of the stomach or at the level of the diaphragm or sometimes involving both sites. In order to eliminate the factor of spasm, five fresh unopened specimens of cardia were fixed in solution of formaldehyde with a small test tube inserted through the cardiac orifice and into the lower part of the esophagus to produce uniform dilatation. These specimens were then opened anteriorly and examined both grossly and by microscopic sections obtained from the anterior and posterior surfaces and from the right and left sides of the cardiac orifice. In no case was there any localized muscular thickening which resembled a sphincter muscle.

I am forced to conclude, therefore, that in the human being there is no morphologic evidence of a sphincter muscle at the cardia. Moreover, the evidence from comparative anatomy would not lead one to expect an anatomic sphincter at this point. Gross and microscopic examinations were made of the juncture of the esophagus and stomach of the fish, salamander, frog, snake, pigeon, hog, calf, rat, mouse, rabbit, guinea-pig, dog, cat and monkey. Only in the group of rodents was localized muscular thickening noted which might be looked on as a cardiac sphincter. In the rat, mouse and guinea-pig this was associated with a reduplication of the mucosa, which apparently functions as a valve to prevent regurgitation from the stomach.

Despite the absence of a sphincter, there is one respect in which the circular fibers at the cardia differ from those in the remainder of the esophagus. This concerns the relationship of the circular fibers to the oblique muscle of the stomach.

In order to reveal by dissection the full extent of the oblique muscle, five unopened specimens of stomach and esophagus were turned inside out. The mucosa was stripped from the surface, and the submucous connective tissue was completely removed by dissection, which exposed the oblique muscle.

The oblique muscle is to be regarded as a special group of inner fibers of the circular muscle of the stomach. It does not form a com-

plete layer in the stomach. On the contrary, it is a U-shaped band, the curve of the U being the loop which passes over the cardiac incisura and the arms of the U being two strands which extend down the lesser curvature on either side of the magenstrasse. The dissections revealed that the oblique fibers loop up into the esophagus for as much as 1 cm. and blend with the circular muscle on the left aspect of the cardia (fig. 3 *A*). At this point the circular and oblique muscles have approximately the same direction and merge sufficiently so that they usually are not readily distinguished in microscopic sections. M'Swiney [21] has observed the same picture in lower animals. What practical significance these facts may have I cannot say. The possibility, however, that overaction of the oblique muscle may exert a pinchcock action on the cardiac orifice seems deserving of consideration in connection with the study of cardiospasm.

THE ELASTIC TISSUE OF THE CARDIA

The elastic tissue of the human esophagus has been carefully described by Schumacher.[22] He did not consider, however, the question of what modifications take place at the cardia. The arrangement of the elastic tissue in the stomach has been summarized by Plenk [17] largely from the studies of Schütz.[23] The work of Schütz on the elastic tissue of the stomach is regarded as the most authoritative, although Schütz based his conclusions on a study of only two stomachs. Schütz seems to have been the only writer to give much attention to the question of the variations in the elastic tissue of different parts of the stomach. He said that in the region of the pylorus the submucosa is richer in elastic fibers than it is elsewhere, while in the region of the cardia there is an increase in the elastic tissue in the sheaths of the muscularis propria. His expression *Cardiaregion,* however, is not sufficiently definite to answer the question of what happens at the cardiac orifice.

The work of Mosher and McGregor [24] in 1928 reopened the question of the arrangement of the elastic tissue around the cardia and raised the question of its clinical significance. These authors said that

21. M'Swiney, B. A.: The Structure and Movements of the Cardia, Quart. J. Exper. Physiol. **19**:237-241, 1929.

22. Schumacher, S.: Die Speiseröhre, in Möllendorff, W.: Handbuch der mikroskopischen Anatomie des Menschen, Berlin, Julius Springer, 1927, vol. 5, pt. 1, pp. 301-336.

23. Schütz, Emil: Zur Kenntnis des elastischen Gewebes des Magens, Arch. f. Verdauungskr. **13**:49-58, 1907; Beiträge zur Histologie des menschlichen Magens, ibid. **14**:241-250, 1908.

24. Mosher, H. P., and McGregor, G. W.: (*a*) A Study of the Lower End of the Esophagus, Tr. Am. Laryng., Rhin. & Otol. Soc. **34**:294-340, 1928; (*b*) A Study of the Lower End of the Esophagus, Ann. Otol., Rhin. & Laryng. **37**:12-70 (March) 1928.

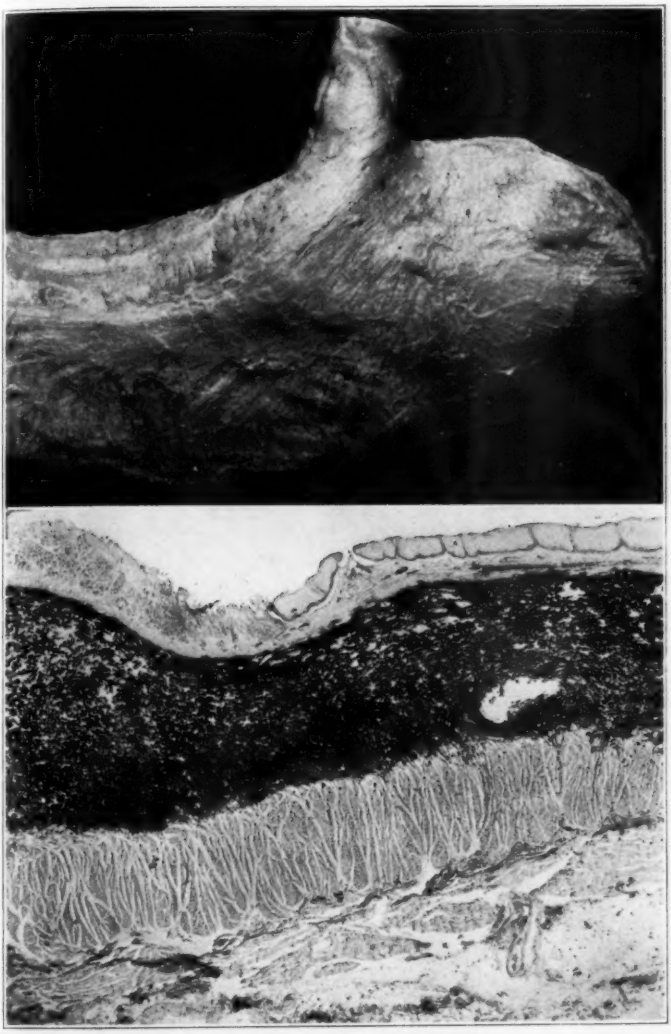

Fig. 3.—*A*, side view of a dissected stomach, showing an arm of the oblique muscle as it extends along one side of the lesser curvature and then loops around the terminal portion of the esophagus to join its fellow of the opposite side. *B*, cross-section showing the injection mixture passing underneath the cardia in the submucosa (× 12).

the elastic tissue of the esophagus is "most abundant in the submucosa, although a certain amount is scattered between the bundles of the two main muscles. The elastic tissue is greatest in amount at the lower end of the esophagus." This is true "even in the disorganized esophagus of cardiospasm" and also in the dog. "The terminal portion of the resting esophagus is closed . . . The deep vertical pleats and the abundant elastic tissue which is present at this point are the main factors in bringing this about." This statement that the elastic tissue functions in the closure of the cardia was made also by Stöhr.[25] He noted an increase in the amount of elastic tissue, however, in the muscular instead of the submucous layer at the cardia.

The issue here raised is of considerable importance. If, as the reports of these authors imply, the closure of the lower end of the esophagus and the cardiac orifice is a passive process caused by elastic tissue and if the opening of the cardiac orifice is the active process, the basic physiologic notions in terms of which writers have tried to explain cardiospasm will need to be radically revised.

In order to throw light on this problem, both longitudinal and transverse sections were taken from the middle portion of the esophagus, cardia, lesser curvature of the stomach and jejunum of five patients examined at necropsy. These specimens were stained with either the Weigert stain for elastic tissue or the Grübler stain for elastin and were examined microscopically.

The observations may be summarized as follows: At the cardia the elastic tissue is essentially the same in amount and arrangement as it is at the middle portion of the esophagus, with one exception, which will be noted presently. The mucosa superficial to the muscularis contains a few fine elastic fibers, which in the adult tend to form sheaths around the cardiac glands. Numerous coarser fibers, longitudinal in direction, are present between the strands of the muscularis mucosae. In the submucosa the elastic fibers, also longitudinal in direction, are more numerous than they are in the mucosa. The bulk of the elastic tissue, however, occurs in sheaths of the muscularis propria. There is an inner sheath between the circular muscle and the submucosa, an intermuscular sheath which splits to surround the ganglions of the myenteric plexus and a ragged and irregular adventitial sheath. The general direction of these sheaths is longitudinal, although numerous circular fibers are noted in connection with the inner circular muscle, and numerous radial strands connect the three layers. The adventitia of the cardia differs from that of the middle portions of the esophagus in that many more

25. Stöhr, Philipp: Lehrbuch der Histologie und der mikroskopischen Anatomie des Menschen mit Einschluss der mikroskopischen Technik, Jena, Gustav Fischer, 1919.

coarse longitudinal fibers are present in the former. The amount of elastic tissue gradually diminishes as sections from the esophagus to the jejunum are examined.

I have been unable to confirm the assertion of Mosher and McGregor that the submucosa of the cardia contains an exceptionally large amount of elastic tissue which functions in the closure of the cardia. Only in the adventitia of the cardia did I observe more elastic tissue than is present in similar sections from the middle portion of the esophagus. The adventitial fibers are longitudinal in direction; hence, they presumably do not have a constrictor action on the cardia.

LYMPHATIC DRAINAGE

My study of the lymphatic drainage at the cardia will be presented in abstract only. The continuity of the submucous space at the cardia was investigated by the method of Horton. In fifteen human specimens a dye and gelatin mixture was injected into the submucosa of the esophagus or of the stomach in the region of the cardia. In contrast to what Horton [26] observed at the pylorus, no submucous block was seen at this orifice of the stomach. The injection mixture passed freely in the submucosa, both from the stomach into the esophagus and from the esophagus into the stomach (fig. 3 *B*).

The lymphatic drainage of the cardia of the living cat was studied by injecting blebs of india ink into the submucosa of the terminal portion of the esophagus and by examining the viscera after intervals of from a half hour to two hours. In all cases drainage was found to occur through the adventitial lymph vessels to one or two lymph nodes at the bifurcation of the trachea and to one or two lymph nodes along the lesser curvature of the stomach. No trace of ink was seen in any other lymph node.

ARTERIAL ANASTOMOSIS

On account of the clinical importance of the esophageal varices which form in cases of portal obstruction, the venous anastomoses across the cardia have long received attention. Recently, Kegaries [1] made a careful anatomic investigation of this subject, and his work called attention to the variability in the amount of venous anastomosis across the cardia and to the richness of the submucous plexus of the esophagus. His

26. Horton, B. T.: Pyloric Musculature with Special Reference to the Pyloric Block, Am. J. Anat. **41**:197-225, 1928; A Study of the Pyloric Block with Special Reference to Musculature, Myenteric Plexus and Lymphatics, Thesis, University of Minnesota Medical School, 1930; Tr. A. Resid. & ex-Resid. Physicians, Mayo Clin. **10**:152, 1930; Pyloric Block with Special Reference to the Musculature, Myenteric Plexus and Lymphatic Vessels, Arch. Surg. **22**:438-462 (March) 1931; footnote 20.

injections showed a band of parallel nonanastomosing veins which connect the submucous venous network of the stomach with that of the esophagus.

Compared with the venous anastomoses, the arterial connections across the cardia have received little attention. Demel,[27] it is true, made a careful investigation of the arterial supply of the esophagus in 1924. Two features of his work, however, made me wish to obtain further enlightenment. First, his method of pumping injection mixture into the aorta and, hence, of injecting the mixture simultaneously into all the arteries which supply the esophagus is not one that outlines sharply the region supplied by any individual artery or that facilitates a comparison of the varying regions supplied in different specimens. Second, he said that the "fourth part of the esophagus reaches from the diaphragm to the cardia and is from 3 to 6 cm. long." In my specimens, however, the length of the esophagus below the diaphragm was generally about 2 cm., which is the figure usually given in the textbooks. The larger figure given by Demel [27] suggested that the "abdominal portion of the esophagus," as defined by its blood supply, may extend considerably farther than the actual subdiaphragmatic segment of the esophagus—a consideration of some importance if true.

My problem was to determine the extent of the arterial connections across the cardia which come from the gastric vessels.

The method employed was that of injecting a radiopaque medium into the left gastric artery. Roentgenograms were made of the arterial tree thus outlined (fig. 4), and dissections were made to determine precisely the position and connections of each vessel revealed in the roentgenograms. Ten human specimens were employed. Great care was taken to eliminate such disturbing factors as the plugging of arteries by blood clots or the presence of pressure or kinking in the region of the cardia.

The most striking single fact demonstrated in the ten specimens was the extreme variability of the arterial connections from the stomach into the esophagus. In some cases the mixture was injected into the esophageal vessels for as far as 10 cm. above the diaphragm. In such cases it is important to note that the esophagus is as richly supplied with vessels as is a similar portion of adjoining stomach. In other cases the mixture stopped abruptly at the cardia, even when the uniform injection of mixture into the stomach indicated that the arterial system was free from blood clots. Most frequently, however, a single branch or a few branches pass from the gastric arteries to supply limited portions of the

27. Demel, Rudolf: Die Gefässversorgung der Speiseröhre: Ein Beitrag zur Oesophaguschirurgie, Arch. f. klin. Chir. **128**:453-504, 1924.

esophagus—not predominantly the right posterior aspect of the esophagus, as Demel [27] has alleged, but portions which vary greatly in size, shape and position.

All the branches of gastric arteries which supply any large portion of the esophagus ascend in the adventitia. The most frequent arrangement is for one large vessel or group of vessels to ascend on the posterior surface of the esophagus and for another vessel or group of vessels to ascend on the anterior surface. These arteries anastomose freely with each other and usually also with the lowest esophageal arteries, which arise from the aorta and which are most frequently seen about 12 cm. above the cardia. I did not make roentgenograms of the diaphragm, but as far as gross dissection could reveal, connection with the diaphragmatic arteries appeared small and infrequent.

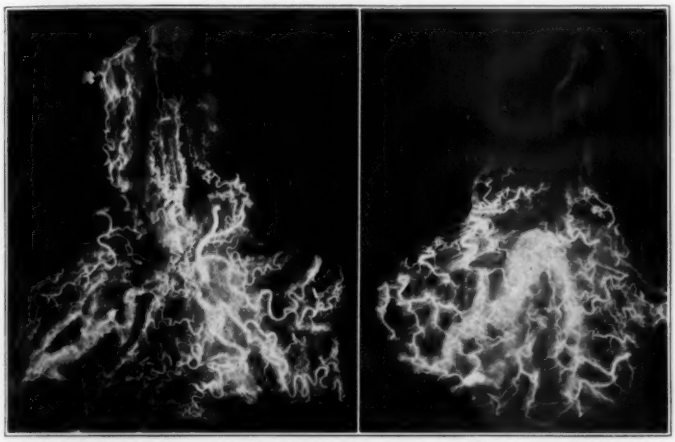

Fig. 4.—Roentgenograms of the arteries of two stomachs, showing the striking difference in the extent of the anastomoses in the lower portion of the esophagus.

The adventitial arteries give off three types of branches: The first type consists of sparse branches which supply the adventitia itself. The second type consists of the numerous but tiny branches which supply the esophageal muscles. These branches generally penetrate to the intermuscular septum and then break up into tiny twigs. The arterial branches which penetrate to the intermuscular septum doubtless communicate with each other and with the arterioles in the intermuscular septum of the stomach, but the anastomoses are so small that I could not demonstrate them in my dissections. The third type of branches of the adventitial arteries consists of relatively large trunks which penetrate through the muscular layer at intervals of about 2 cm. and enter the

submucosa. In the submucosa they break up into a fine network of anastomoses which resemble the venules of a leaf. At the cardia this network communicates freely with the submucous plexus of the stomach. There is no band of straight nonanastomosing vessels connecting the two networks across the cardia, such as Kegaries has observed in the venous anastomosis. On the contrary, the same architecture is observed in the network which crosses the cardia as in the adjoining esophagus and stomach. It is important to note, however, that the anastomoses in the submucosa are fine and hairlike and incapable of carrying the injection mixture more than a couple of centimeters up the esophagus if the adventitial arteries are occluded.

NERVES (MYENTERIC PLEXUS)

If there is no sphincter or muscular discontinuity at the cardia to explain the functional changes which occur at this point, one must look for their explanation in the nervous mechanisms of the cardia. Even if the controversial phenomenon of clinical cardiospasm is left out of consideration, it must be recognized that the cardia is the site of important changes in function that distinguish this region not only from the adjoining stomach but also from the portions of the esophagus which lie above it. First, there is the action as a physiologic sphincter. Second, there is the phenomenon of experimental spasm of the circular muscle at the cardia (not necessarily identical with clinical cardiospasm), which may be produced by cutting the vagi or reflexly by stimulating various abdominal viscera, as Carlson, Boyd, Pearcy and Luckhardt,[28] Scrimger,[29] and others have demonstrated. Third, although Alvarez [30] stated the opinion that the peristaltic waves of swallowing may pass across the cardia and continue as peristaltic waves of the stomach, it is obvious that there is a discontinuity at the cardia between the rapid and voluntarily initiated waves of swallowing and the slower and rhythmic movements of the stomach.

The myenteric plexus (Auerbach's plexus) is a network of nerve fibers, mostly unmyelinated, which lies between the inner circular and outer longitudinal muscular layers of the enteric canal and which

28. Carlson, A. J., and Luckhardt, A. B.: Studies on the Visceral Sensory Nervous System: X. The Vagus Control of the Esophagus, Am. J. Physiol. **57**: 299-335 (Sept.) 1921. Carlson, A. J.; Boyd, T. E., and Pearcy, J. F.: Studies on the Visceral Sensory Nervous System: XIII. The Innervation of the Cardia and the Lower End of the Esophagus in Mammals, ibid. **61**:14-41 (June) 1922; XIV. The Reflex Control of the Cardia and the Lower Esophagus in Mammals, Arch. Int. Med. **30**:409-433 (Oct.) 1922.

29. Scrimger, F. A. C.: Idiopathic Dilatation of the Oesophagus, Ann. Surg. **94**:801-817 (Nov.) 1931.

30. Alvarez, W. C.: Personal communication to the author.

extends from the upper portion of the esophagus to the terminal portion of the rectum. This plexus is uniformly distributed on all sides of the alimentary canal. At the nodal points of the network, ganglions occur. Krishnan [31] and others have demonstrated that the myenteric plexus functions to control or at least to coordinate the movements of the gastro-intestinal tract.

The myenteric plexus presents the same appearance at the cardia as it does throughout the lower two thirds of the esophagus. It is cut about once a millimeter in microscopic sections passing through the intermuscular septum. It is a less conspicuous structure at the cardia than it is in the small intestine, because it is surrounded by connective tissue instead of lying naked between the muscular layers. The ganglions are made up of nerve fibers, ganglion cells and sustentacular cells. I have tried a wide variety of special stains but have not found any that can approach the ordinary Van Gieson stain in rendering the ganglion cells easily visible so that the cells can be counted.

Ganglion cells appear in variable numbers in the ganglions at the cardia; occasionally, a favorable section may show as many as ten cells in one ganglion. They are roughly oval, with the long axis parallel to the long axis of the esophagus. When stained with the Van Gieson stain they present a striking appearance. They are far larger than any other cells which may be seen in this region. The cytoplasm, which stains a dark brownish gray, is equally distinctive. The large, clear nuclei, each with a large nucleolus, are also specific. Finally, each ganglion cell is surrounded by a capsule of sustentacular cells. The latter, which have numerous other names, are apparently insulating cells which correspond to the cells of the sheath of Schwann and the oligodendroglia cells in the peripheral nerves and the central nervous system, respectively.

Dogiel [32] described two types of ganglion cells in the myenteric plexus, the distinction resting chiefly on the differences in the dendrites, as revealed by the vital methylene blue stain. He said that one type represents ganglion cells of the sympathetic system and that the other type represents ganglion cells of the vagus nerve. The evidence on the subject has been critically evaluated by Gaskell [33] and more recently by Kuntz.[34] The weight of authority favors the view that all the ganglion

31. Krishnan, B. T.: Studies on the Function of the Intestinal Musculature: Are Intestinal Movements Neurogenic or Myogenic? Quart. J. Exper. Physiol. **22**:361-368 (June) 1933.

32. Dogiel, A. S., quoted by Gaskell.[33]

33. Gaskell, W. H.: The Involuntary Nervous System, London, Longmans, Green & Co., 1916.

34. Kuntz, Albert: The Autonomic Nervous System, Philadelphia, Lea & Febiger, 1929.

cells of the myenteric plexus in the esophagus, cardia and stomach represent terminal ganglion cells of the vagus nerve. Sympathetic fibers are not present in the esophagus, except in the last few centimeters above the cardia. Here, they mingle with the fibers of the myenteric plexus but pass through the ganglions without synapse. There is certain physiologic evidence which indicates the presence of independent local reflex arcs in the wall of the intestine, which are mediated by the myenteric plexus. The anatomic evidence is all against such a view, however.[35]

The question of the continuity of this nervous network from the esophagus into the stomach has a good deal of physiologic significance, yet I have found that only two authors have investigated the subject. One was Irwin,[36] who used the vital methylene blue technic; who reported that in the guinea-pig he had traced some nerve fibers from the esophagus to ganglions in the stomach. The second author was Sir Arthur Keith. After discovering in the heart the node which now bears his name—the sino-auricular node—Keith [37] began to find similar nodes almost everywhere. He has described several of them situated at strategic points in the gastro-intestinal tract. Among other places he claimed to have found a "definite development of neuromuscular junctural tissue" at the cardia. No other anatomist has confirmed Keith's work. His illustrations look to me like those of an ordinary myenteric plexus. None of my sections of the cardia showed any structure that could be interpreted as neuromuscular junctural tissue. One can hardly escape feeling that the junctural node at the cardia belongs in the same category as the unicorn and the basilisk.

As will be demonstrated in a later section of this paper, lesions of the myenteric plexus are an important subject in relation to the pathogenesis of cardiospasm. The lesions are ordinarily described in terms of numerical loss of ganglion cells as seen in microscopic sections of the myenteric plexus. It is accordingly important to establish a norm for the number of ganglion cells appearing in a standard microscopic section. But before this is done, it is necessary to point out that if the

35. Alvarez, W. C.: The Mechanics of the Digestive Tract: An Introduction to Gastroenterology, New York, Paul B. Hoeber, Inc., 1928.

36. Irwin, D. A.: The Anatomy of Auerbach's Plexus, Am. J. Anat. **49**:141-166 (Sept.) 1931.

37. Keith, Arthur: An Account of Six Specimens of the Great Bowel Removed by Operation, with Some Observations on the Motor Mechanism of the Colon, Brit. J. Surg. **2**:577-599, 1915; A New Theory of Enterostasis, Lancet **2**:371-375 (Aug. 21) 1915; Discussion on the Interpretation of Certain X-Ray Signs of Intestinal Stasis, Proc. Roy. Soc. Med. (Electrotherap. Sect.) **9**:1-11, 1916; The Great Bowel, from an Anatomist's Point of View, in Lane, W. A.: The Operative Treatment of Chronic Intestinal Stasis, ed. 4, London, Hodder & Stoughton, 1918, pp. 202-217.

ganglion cells of the myenteric plexus, like those elsewhere in the body, do not increase in number after birth, then the esophagus in the adult can contain no more ganglion cells than the esophagus of the new-born infant. This same number of ganglion cells, moreover, is distributed over a longer and wider esophagus in the adult, and fewer cells can be expected to appear in a microscopic section of given dimensions. Furthermore, in the dilated esophagus in a case of cardiospasm the mean distance between ganglion cells must be still further increased, and even without any destruction of ganglion cells one must expect the number of cells in any microscopic section to be greatly reduced.

In order to determine the normal number of ganglion cells to be expected in a microscopic section at the cardia, counts were made on two hundred segments of the myenteric plexus appearing in sections of the cardias of fifty-eight adults. In all cases the cardia appeared grossly and microscopically normal. The fifty-eight persons included forty-one men and seventeen women. The range in age for the men was from 22 to 87 years, with an average age of 56.85 years. The range in age for the women was from 18 to 78 years, with an average age of 48.17 years. In these fifty-eight cases eighty-nine blocks of tissue were taken. One hundred and thirty-nine sections were made. The sections were 8 microns thick and were cut in a longitudinal direction, perpendicular to the surface. The sections were mostly stained by the Van Gieson method. According to the length of the section, one or two segments, which were 1 cm. in length, were measured along the myenteric plexus and marked on the cover glass, and the number of ganglion cells present in such segments was counted with the aid of a microscope. It will be understood that not every ganglion cell was cut squarely through the center in such a way as to reveal all its characteristic features. Only such structures were counted as ganglion cells, however, as were sufficiently intact to be identified unquestionably as such. Twelve hundred and fifty ganglion cells were counted in 200 segments, which were 1 cm. long. The results are presented in table 1. The curve that shows the frequency of these cells has an interesting skew shape (fig. 5). The wide range of the various counts and the large probable error emphasize the necessity for making multiple counts of cells before concluding that the number of ganglion cells is abnormal in cardiospasm or in any other condition.

The range of values found when multiple counts were made with sections from a single cardia confirms these conclusions. A comparison of the number of ganglion cells in specimens obtained from a small group of young adults with the number of ganglion cells in specimens obtained from a similar group of aged adults suggested that there may be some loss of ganglion cells with advancing years.

CARDIOSPASM

Some of the anatomic features of the normal cardia have already been described. It is now my intention to apply these norms to the study of specimens from patients with cardiospasm. It is my purpose

TABLE 1.—*Data on the Number of Ganglion Cells in Centimeter Segments of the Myenteric Plexus at the Cardia* *

Number of Ganglion Cells	Number of Times Observed	Number of Ganglion Cells	Number of Times Observed
0	24	16	5
1	19	17	4
2	18	18	1
3	16	19	1
4	16	20	1
5	18	21	1
6	11	22	1
7	7	23	1
8	12	24	0
9	10	25	0
10	8	26	0
11	6	27	0
12	9	28	0
13	4	29	1
14	4	30	0
15	2		

* Segments counted, 200; ganglion cells counted, 1,250; mean number of ganglion cells per segment, 6.25; mode, 0; standard deviation, ±5.48; probable error, ±3.69.

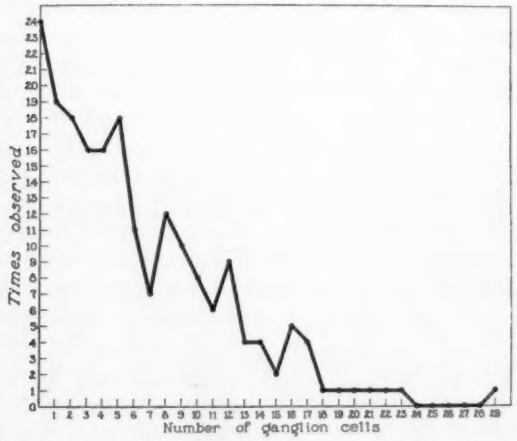

Fig. 5.—Graph showing the frequency of ganglion cells in segments of the myenteric plexus 1 cm. in length.

to lay aside clinical preconceptions as to the nature of cardiospasm and to study the available material simply as examples of a chronically dilated esophagus without evident organic obstruction. Even the report of clinical histories will be reduced to the minimum of facts, such as

the duration of symptoms, operative treatment and coincidence with the onset of some acute infectious disease, which are directly pertinent to the interpretation of the anatomic findings.

Hurst recently has pushed the history of cardiospasm back a century and a half by calling attention to a remarkable case recounted in 1672 by Thomas Willis [38] in his "Pharmaceutice rationalis." Willis not only divined the true nature of the condition but even treated it successfully with dilation. The honor of describing the first case of idiopathic dilatation of the esophagus, however, is usually attributed to Purton [39] in 1821. Hannay [40] (1833) is generally credited with the second case, although Herbert Mayo [41] performed a necropsy in one case in 1829. Zenker [42] and von Ziemssen were the first to recognize the condition as a clinical syndrome (in 1876). They collected reports of seventeen cases from the literature and applied to the disease the name simple ectasia of the esophagus. Following this numerous cases were reported, chiefly from Germany, but it remained for Plummer [43] and his associates to appreciate the great clinical importance of cardiospasm and to discover highly accurate methods of diagnosis and a satisfactory procedure of treatment. The literature on cardiospasm was reviewed in German in 1921 by Thieding [9] and in English in 1933 by Sturtevant.[44]

In 1882 von Mikulicz [45] coined the catchy but question-begging term cardiospasm. This name is as unfortunate as would have been the designation anospasm for Hirschsprung's disease, because the view that chronic dilatation of the esophagus results from a spasm of the circular muscle at the cardia is by no means universally accepted. For example, Bassler [46] has said that what is called cardiospasm is in reality a constriction of the lower end of the esophagus by the crura of the

38. Willis, T., quoted by Hurst.[71b]

39. Purton, J., quoted by Sturtevant.[44]

40. Hannay, A. J.: An Extraordinary Dilatation (with Hypertrophy) of All the Thoracic Portion of the Esophagus, Causing Dysphagia, Edinburgh M. & S. J. **40**:65-72, 1833.

41. Mayo, Herbert: Outlines of Human Pathology, Philadelphia, A. Waldie, 1839.

42. Zenker, F., in von Ziemssen, H.: Handbuch der speciellen Pathologie und Therapie, Leipzig, F. C. W. Vogel, 1876.

43. Plummer, H. S.: Cardiospasm with Report of Cases, J. Minnesota M. A. **26**:419-424, 1906; Cardiospasm with Report of Forty Cases, J. A. M. A. **51**:549-554 (Aug. 15) 1908.

44. Sturtevant, Mills: Cardiospasm, with a Review of the Literature, Arch. Int. Med. **51**:714-736 (May) 1933.

45. von Mikulicz, J., quoted by Sturtevant.[44]

46. Bassler, Anthony: Cardiospasm: What It Is; What It Seems to Be, New York State J. Med. **14**:9-11, 1914.

diaphragm. Chevalier Jackson [47] and others have further developed this theory and have suggested that this clinical syndrome be termed phrenospasm. Zenker,[42] Rosenheim,[48] Bier [49] and Sternberg,[50] however, have asserted that in cardiospasm the cardia is no more firmly closed than it normally is but that the failure is the result of paralysis of the esophagus, so that the function of forcing food through the cardiac orifice is not exercised. Hurst stated that the "law of the intestine" applies at least to the cardiac end of the esophagus and gave as his opinion that so-called cardiospasm is really a failure of the normal reflex relaxation of the cardia in swallowing. Accordingly, he applied to the condition the term achalasia of the cardia. Mosher has entertained at various times the theories that the obstruction to swallowing is caused by pressure on the esophagus by the tips of the lungs, by compression by the "liver tunnel," [51] by kinking and torsion of a redundant esophagus [52] and by fibrosis of the periesophageal connective tissue.[53]

The study of cardiospasm is handicapped by something which impedes the study of few diseases, namely, the extraordinary effectiveness of the methods available for treatment. Despite the frequency of the condition, so few persons die of cardiospasm at the various medical centers that I have found no reports of necropsy which comprise more than thirteen cases.

Some evidence has accumulated, however, to support the view that cardiospasm is associated with definite lesions of nerves. Cameron [54] has reported lesions of Auerbach's plexus in seven cases of cardiospasm in children. Heyrovsky [55] noted vagus neuritis at necropsy in cases of cardiospasm, and Loeper and Forestier [56] have reported recurrent spasm

47. Jackson, Chevalier: The Diaphragmatic Pinchcock in So-Called "Cardiospasm," Laryngoscope **32**:139-142 (Feb.) 1922.

48. Rosenheim, T., quoted by Sturtevant.[44]

49. Bier, August: Die Erklärung der Ischuria paradoxa und des Kardiospasmus, Zentralbl. f. Chir. **58**:901-902 (April 11) 1931.

50. Sternberg, W., quoted by Sturtevant.[44]

51. Mosher, H. P.: Liver Tunnel and Cardio-Spasm, Laryngoscope **32**:348-362 (May) 1922.

52. Mosher, H. P.: Cardiospasm, Pennsylvania M. J. **26**:240-249 (Jan.) 1923.

53. Mosher, H. P.: Fibrosis of the Terminal Portion of the Esophagus: Cardiospasm, Proc. Internat. Assemb. Inter-State Post-Grad. M. A., North America **6**:95-104, 1931.

54. Cameron, J.: Oesophagectasia in a Child, Arch. Dis. Childhood **2**:358-360 (Dec.) 1927.

55. Heyrovsky, Hans: Casuistik und Therapie der idiopathischen Dilatation der Speiseröhre: Oesophagogastroanastomose, Arch. f. klin. Chir. **100**:703-715 (Jan. 30) 1913.

56. Loeper, M., and Forestier, J.: Les lésions nerveuses du pneumogastrique et le cardiospasme récurrent dans le cancer de l'estomac, Arch. d. mal. de l'app. digestif **11**:307-312, 1921.

at the cardia in carcinoma of the stomach that was complicated by ascending invasion of the vagus by tumor cells. Kraus and Pollitzer [57] also have reported lesions of the vagus nerve in cardiospasm. Finally, Hurst and Rake,[58] Stokes,[59] Rake,[60] Cameron,[54] Beattie [61] and Mosher and McGregor have reported a loss of ganglion cells in the myenteric plexus in cases of cardiospasm. Whether this is primary or secondary is a controversial point. Mosher, who already has an excess of theories with which to explain cardiospasm, stated that he was inclined to think that the loss of ganglion cells is secondary to the pressure which the distended esophagus suffers. He quoted Cannon [12] to show that the ganglion cells of the myenteric plexus are highly susceptible to pressure anemia. Hurst, on the other hand, concluded that "achalasia of the cardia," as he termed the condition, is primarily an organic disease of Auerbach's plexus.

Cardiospasm is frequently associated with diverticulum of the esophagus. Sturtevant listed Vinson,[62] Fitzgibbon,[63] Bull,[64] Dufour,[65] Van den Wildenberg [66] and Freud [67] as reporting cases of this concurrence. The association of cardiospasm with asthma has been noted by Scollery,[68] von Bergmann [69] and Lindvall.[70] The condition most commonly found in association with cardiospasm, however, is peptic ulcer. Heyrovsky [55] and many others have commented on this fact. Syphilis is not often found in conjunction with cardiospasm, and in none of the following cases was syphilis present.

REPORT OF CASES

The specimens in the following thirteen cases were examined grossly, and from twenty-five to one hundred sections of each specimen afterward were studied microscopically. Each case will be described briefly, and then the findings for the whole group will be summarized.

57. Kraus and Pollitzer, quoted by Mosher and McGregor.[24a]

58. Hurst, A. F., and Rake, G. W.: Achalasia of the Cardia (So-Called Cardiospasm), Quart. J. Med. **23**:491-508 (July) 1930.

59. Stokes, A., quoted by Hurst.[71b]

60. Rake, G., quoted by Hurst.[71b]

61. Beattie, W. J. H. M., quoted by Hurst.[71b]

62. Vinson, P. P.: Cardiospasm Associated with Esophageal Diverticula, New York M. J. **117**:540 (May 2) 1923.

63. Fitzgibbon, J. H., quoted by Sturtevant.[44]

64. Bull, P. N., quoted by Sturtevant.[44]

65. Dufour, H., quoted by Sturtevant.[44]

66. Van den Wildenberg, L., quoted by Sturtevant.[44]

67. Freud, J., quoted by Sturtevant.[44]

68. Scollery, quoted by Sturtevant.[44]

69. von Bergmann, quoted by Sturtevant.[44]

70. Lindvall, H., quoted by Sturtevant.[44]

CASE 1.—A man aged 53 had suffered from salivation and progressive dysphagia for five years before he came to the Mayo Clinic. A roentgenogram revealed not only dilatation of the esophagus but a perforating ulcer on the lesser curvature of the stomach. The ulcer was excised, and the cardia was manually dilated in the course of the operation. The patient made an uneventful convalescence. Eleven days after the operation he was dismissed from the hospital and was waiting for a bus, when he suddenly dropped dead on the sidewalk.

The general observations at necropsy included old healed aortic and mitral endocarditis with stenosis; hypertrophy and dilatation of the heart; arteriosclerotic changes in the kidneys; fatty changes in the heart, liver and kidneys; multiple diverticula of the rectum; moderate general arteriosclerosis, and thrombosis of the prostatic plexus. The partial excision by knife of the gastric ulcer had healed without perforation or peritonitis. Death was attributed to cardiac failure.

Examination of the stomach and esophagus revealed contraction without organic narrowing of the lowest 4 cm. of the esophagus. There was a fusiform dilatation, which proceeded from below upward to a sac which had a maximal inner circumference of 8 cm. at a point 9 cm. above the juncture of the esophageal and the gastric mucosa. There was no evidence of ulceration, scarring or rupture of the esophagus; no diverticulum, twisting or kinking of the esophagus was present, and there was no suggestion of a hypertrophied sphincter or of hypertrophy of the oblique muscle of the stomach.

Microscopic examination showed that in the undilated portion of the esophagus, at and just above the cardia (I shall call this portion the neck), the epithelium was relatively thickened, but otherwise it was normal. In the dilated portion of the esophagus (the sac) the epithelium was thinner and was eroded in some places but not ulcerated. The neck revealed a relative thickening of both layers of the muscularis propria and a slight increase in the amount of elastic tissue. In the sac the amounts of muscle and of elastic tissue were approximately normal, but the circular elastic fibers were more prominent than usual. There was no fibrosis among the muscle fibers. The ganglion cells of the myenteric plexus had almost disappeared (fig. 6). No cells were seen in sixteen segments of the cardia, which were 1 cm. in length, and in nine similar segments of the sac. The ganglions of the myenteric plexus showed a great increase in the number of nuclei in the supporting (sustentacular) cells. These cells frequently formed little whorls inside what appeared to be the capsules of former ganglion cells. Such whorls presented a superficial resemblance to renal glomeruli; for want of a better label they will be termed glomeruloids. As was true in many of these cases, the largest part of the vagus nerve had been removed by the laboratory technician in the process of making a neat looking specimen for display. Numerous fragments of the vagus plexus were discovered, however, and studied with special stains for nerves, but all were normal.

CASE 2.—A woman aged 29 came to the clinic because of dysphagia, which had been present for two years. In the previous six months she had undergone ten dilations of the esophagus for cardiospasm. Seven days before she came to the clinic she had submitted to dilation elsewhere, which had been followed by fever and soreness and swelling of the neck. At the time the patient came to the clinic advanced cellulitis of the neck, stridor, dyspnea and cyanosis were present. She died the following day.

Necropsy revealed rupture at the upper end of the esophagus, with multiple and extensive communicating retropharyngeal and pretracheal abscesses. Thy-

roidectomy, which had been performed ten years previously, was found to have left extensive scars around the trachea and carotid sheaths. The examination did not reveal anything else of consequence.

Examination of the specimen did not reveal organic constriction of the neck of the cardiospasm. It extended for about 1 cm. above the mucosal junction. There was a fusiform dilatation that extended to a sac, which was 28 cm. long but only 5.4 cm. in its greatest circumference. The walls of the sac were thick, and the mucosa was puckered in the lower portion. On the left side of the esophagus, 1.2 cm. below the cricoid cartilage, was a perforation which measured 1 by 4 mm. There was no evidence of ulceration, kinking, scarring or diverticulum of the esophagus.

Microscopic study disclosed that the epithelium was normal throughout, except for a few erosions. There was no ulceration. Sections through the edges of the perforation demonstrated that the rupture was through the sound esophagus and

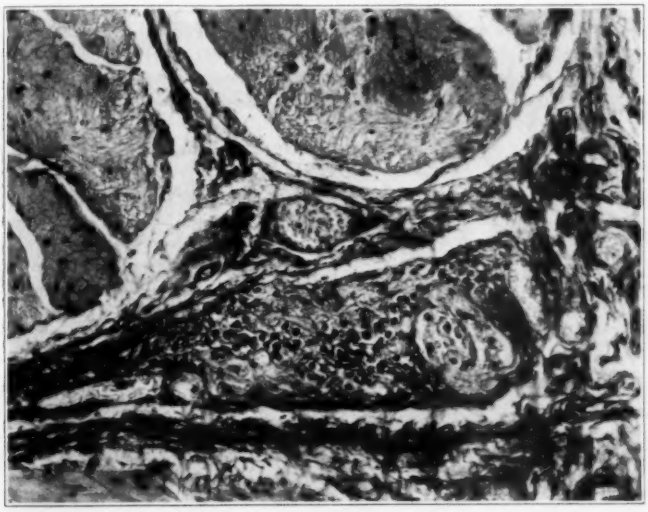

Fig. 6.—A ganglion in the myenteric plexus in case 1 (× 235). Ganglion cells are absent, and the proliferating cells have taken on an appearance which some observers have confused with that of lymphocytes. At the right is an imperfect example of one of the whorls of cells which I have labeled a glomeruloid.

that it had not been preceded by scarring or ulceration. The edges of the perforation were the site of a violent pseudomembranous inflammation. Diffuse inflammation, with many polymorphonuclear leukocytes, had spread in the mucosa as far as the cardia. It had not spread so far in the intermuscular septum, but it involved the myenteric plexus. Infection had extended a still smaller distance in the submucosa and in the adventitia. Both muscular layers were greatly thickened throughout the entire length of the sac, and the circular muscle measured 0.5 cm. in thickness. The muscle did not reveal any fibrosis or special band at the cardia. The density of the elastic tissue was increased in the lower two thirds of the esophagus, but it became thin in the upper third. Ganglion cells had mostly disappeared; none were seen in three segments of the cardia, and only two were

present in seventeen segments of the sac. In the lower part of the esophagus the ganglions showed proliferation of supporting cells and the formation of glomeruloids; in the upper part the ganglions were involved in acute inflammation. The vagus nerve appeared normal on section.

CASE 3.—A woman aged 39 had suffered from increasing difficulty in swallowing for seventeen years, with regurgitation of undigested food after eating. Dilation of the esophagus was followed at once by colic and evidence of pleuritis on the left side. The following day 1,200 cc. of fluid was aspirated from the left pleural cavity. Afterward posterior mediastinotomy was performed for rupture of the esophagus. Two days later subcutaneous emphysema of the neck developed. The patient died on the seventh day after the operation.

Necropsy revealed rupture of the esophagus, widespread mediastinitis, empyema on the left side, collapse of the left lung, recent resection of the ninth and tenth ribs on the left side posteriorly and terminal pleuritis at the base of the right lung. Old healed tuberculous pleuritis and lymphadenitis, cysts of the ovaries, polyps of the uterus, papillomas of the bladder, Meckel's diverticulum and moderate arteriosclerosis also were noted. The esophagus was dilated. The laceration, which was 1.5 cm. long, was longitudinal in direction and extended upward from a point 1.5 cm. above the mucosal junction. Considerable thickening of the neighboring diaphragm was noted.

No gross organs could be removed; hence my study was limited to small fragments of tissue which showed the rupture and thickening of the mucosa of the terminal portion of the esophagus. Microscopic study showed the epithelium to be thickened, with beginning cornification, which was of the mucous membrane type. No ulceration was present. Sections from the borders of the tear in the esophagus showed it to be the site of acute pseudomembranous inflammation. There was no evidence of old ulceration or thinning of the muscular layers at this point. The infection had extended for some distance in the submucosa. The strands of the circular muscle, just above the cardia, appeared to be pulled apart and showed regions of necrosis without infection. As will be demonstrated later, this appearance of the circular muscle is not infrequently found in cases of cardiospasm after dilation. There was no fibrosis in the muscular layers, and the elastic tissue appeared normal. In twenty-three segments of the myenteric plexus, which were 1 cm. in length and from the cardia, a total of thirteen ganglion cells were seen, most of them in various stages of degeneration. There was an increase in the number of nuclei in the supporting cells in the ganglions, and numerous glomeruloids were seen. Sections from the vagus nerve were normal.

CASE 4.—A youth aged 17 years always had been regarded as enjoying perfect health. When his mother was questioned in the light of the postmortem observations, however, she related that ever since childhood he had been accustomed to regurgitate food after eating. The food had come up easily and without retching. He had learned not to eat too much at a time and to keep a basin beside him while he ate. On Sept. 23, 1924, the patient had engaged in football practice until 6 p. m. He had remained with his companions until 7 p. m. and then had come home. His parents had found him dead on the floor at 9 p. m. There had been spontaneous evacuation of the bowels and bladder. A medicolegal necropsy was performed by Dr. H. E. Robertson. The esophagus was observed to be dilated and its wall was somewhat hypertrophied. There was generalized lymphadenopathy, but none of the lymph nodes was more than 1 cm. in diameter. Arteriosclerosis was slight. The remainder of the examination, including the examination of the brain and of the organs of the neck, and toxicologic examination of the gastric contents, did not reveal anything to explain the cause of death.

The esophagus was dilated almost the entire distance from the cardia to the cricoid cartilage. Its size was normal for about 1.5 cm. above the juncture with the gastric mucosa; then there was gradual dilatation to a maximal circumference of 8 cm. at a point 9 cm. above the cardia. The thickness of both the mucosal and the muscular layer was increased in the lower part of the esophagus but normal above. No diverticulum, ulceration or evidence of kinking or twisting of the terminal portion of the esophagus was noted. No special sphincteric muscular band or increased prominence of the oblique muscle of the stomach was observed.

Microscopic study revealed a general thickening of the epithelium. No ulceration or inflammation was present. Both muscular layers were thickened in the neck and in the lower part of the sac; the circular muscle had attained a thickness of 4 mm. In the upper part of the sac the thickness of the muscle was normal. Some vacuolar degeneration was present in the thickened circular muscle, but there was no fibrosis. The elastic tissue was slightly more prominent than normal. There was a general loss of ganglion cells in the myenteric plexus; eight segments of the cardia and lower and middle portions of the sac revealed a total of only three ganglion cells. At the upper end of the esophagus two segments revealed two and five ganglion cells, respectively. The degree of the proliferative changes in the ganglions was only moderate. No specimen of the vagus nerve could be obtained.

CASE 5.—A woman aged 66 came to the clinic after she had suffered for eight years from intermittent attacks of dysphagia and salivation. During the previous eighteen months the symptoms had become much worse. Dilation of the cardia was followed at once by substernal discomfort. The following day there was severe abdominal pain, and the next day auricular fibrillation, pleural effusions on both sides, dyspnea and paralysis of the left arm were present. The patient died on the third day after the operation.

Necropsy revealed that the esophagus had ruptured in the course of dilation and that there were consequent mediastinitis, bilateral empyema and purulent peritonitis of the lesser peritoneal sac. Mural thrombi were present in the left ventricle, and a diagnosis of multiple cerebral emboli was made on the basis of the clinical findings. Advanced emaciation, old healed tuberculous pleuritis and lymphadenitis, moderate arteriosclerosis, atrophy of the liver and arteriosclerotic changes in the kidneys also were noted.

The esophagus was dilated to a fusiform sac, which had a maximal circumference of 8 cm. at a point 11 cm. above the cardia. The circumference of the lower few centimeters of the esophagus was approximately normal. Beginning 0.5 cm. above the mucosal junction on the left side of the esophagus, there was a longitudinal tear 2.5 cm. in length. Several large lymph nodes were seen around the esophagus. No ulceration, diverticulum or evidence of kinking of the terminal portion of the esophagus was observed.

Microscopically the epithelium was observed to be thickened near the cardia; it was eroded but not ulcerated in the sac. The rupture passed through a region where the mucosa and muscular layer previously had been normal. The edges of the rupture were covered with acute pseudomembranous inflammation. Violent infection and inflammation, with necrosis, hemorrhage and masses of polymorphonuclear leukocytes, had spread in the submucosa, in the intermuscular septum and especially in the adventitia of the esophagus for a long distance as a result of the rupture. Both muscular layers were thickened in the neck and in the lower portions of the sac. There was no fibrosis of the muscular layer. The elastic tissue was normal throughout, except that the circular fibers were a little more prominent

than normally in the sac. Ganglion cells were numerous in the myenteric plexus of the stomach, near the cardia, but there were none in the terminal portion of the esophagus and in the sac of the cardiospasm. No ganglion cells were seen in twenty-five segments of the neck and of the lower and middle portions of the sac. At the extreme upper end of the esophagus, however, twenty-one ganglion cells were seen in five segments. There appeared to be little proliferation of the supporting cells, but the widespread infection in the intermuscular septum following the rupture made this difficult to judge. Sections of the vagus nerve were normal.

CASE 6.—A girl aged 8 years had begun to have increasing esophageal obstruction after whooping cough three years before she was brought to the clinic. For a year and a half the obstruction had been extreme. When she arrived at the clinic she was too weak to allow any manipulation, and she died six days later.

Necropsy revealed advanced dilatation and hypertrophy of the esophagus, extreme emaciation and terminal bronchopneumonia, with edema of the glottis.

The circumference of the lowest 1.5 cm. of the esophagus was about normal (2.5 cm.). Above this there was gradual dilatation to a circumference of 7.5 cm. at a point 7 cm. above the cardia. The total length of the sac was 16 cm. On the left anterior surface of the sac there was a scar measuring about 2.5 by 0.3 cm., which was longitudinal in direction. It extended through all layers of the esophagus and involved a lymph node externally. Within a few centimeters of the scar were eight lenticular ulcers of the mucous membrane, each measuring about 0.5 by 0.2 cm. There was no diverticulum or kinking of the esophagus.

Microscopic examination showed a thickening of the epithelium, especially in localized islands. The ulcers which have been mentioned were subacute or chronic. They penetrated the muscularis mucosae and rested on the circular muscular layer. From the bases of each ulcer, strands of lymphocytes and endothelial cells extended between the muscular bundles to the intermuscular septum. Traces of the same infectious process were observed throughout the entire esophagus, in the submucosa, between the muscular bundles and in the adventitia, but especially in and around the ganglions of the myenteric plexus. Both muscular layers were increased in thickness. There was a slight increase in the amount of connective tissue in the septum of the circular muscular layer. Twenty-five segments of the cardia and sac did not reveal any ganglion cells; these segments were 1 cm. long. Besides the chronic infection (which may apparently be traced to the myenteric plexus from the ulcers of the mucosa), the ganglions were enmeshed in much hyaline scar tissue. Sections from the vagus nerve appeared normal.

CASE 7.—A man aged 58 had suffered from dysphagia for twenty years, and regurgitation of food and water had occurred for five years. Dilation of the cardia was accompanied with slight pain and bleeding. An hour later he vomited blood and complained of severe pain in the abdomen and in the left side of the thorax. He failed rapidly and died on the second day after the operation.

Necropsy disclosed that a rupture of the esophagus had been followed by hemorrhage and pleurisy in the left pleural cavity. The left lung was totally collapsed and covered with grayish white exudate. Advanced emaciation, old healed tuberculous pleuritis and pneumonitis and a small adenoma of the thyroid gland also were present.

The esophagus was greatly thickened but moderately dilated, the greatest circumference being 5.6 cm. at a point 10.8 cm. above the cardia. The transition from the neck to the sac was gradual. Beginning 0.8 cm. below the mucosal junction with the stomach, there was a longitudinal split which was 3.2 cm. long

and extended up the esophagus. Only the upper centimeter of this tear extended entirely through the muscular wall. There was no diverticulum, ulceration or kinking of the esophagus.

Microscopic study showed that the epithelium was moderately thickened throughout. There was no cornification or ulceration. The rupture did not involve an old ulceration or defect in the muscular wall. The edges of the tear were covered with pseudomembrane. Acute infection and hemorrhage had spread from the tear a long distance in the adventitia, in the intermuscular septum and especially in the submucosa, where the phlegmon had reached the middle portion of the esophagus. The spread of hemorrhage and infection had stopped abruptly at the junction with the stomach. In the neck of the cardiospasm there was patchy hemorrhage in the circular muscle. There was also necrosis of portions of muscle which were involved in the phlegmon. An extremely small amount of old fibrosis was present in the strands of muscular fibers near the cardia. Both muscular layers were thickened throughout the entire esophagus, and the circular muscle had attained a thickness of 3.5 mm. The elastic tissue was about normal everywhere, although the circular fibers were relatively more prominent in the sac than elsewhere. Although the ganglion cells were normal in the adjoining stomach, they had practically disappeared in the myenteric plexus of the esophagus. Only three ganglion cells were observed in twenty-three segments of the myenteric plexus. In the lower half of the esophagus the ganglions were involved in the infection which had spread from the rupture; in the upper half the ganglions exhibited much proliferation of supporting cells but were not infected. Sections of the vagus nerve were normal.

Case 8.—A man aged 50 had complained of dysphagia and regurgitation, with increasing emaciation, for two years. He had uremic symptoms when he arrived at the clinic. A stomach tube was passed, but he became irrational and pulled it out. He failed rapidly and died a few days later.

Besides the dilatation and hypertrophy of the esophagus, necropsy revealed bilateral bronchopneumonia, with a small abscess on the right side; a hemangioma of the left vocal cord; an old healed duodenal ulcer; cholelithiasis, cholecystitis and dilatation of the gallbladder; Meckel's diverticulum; melanosis coli; advanced arteriosclerosis; old healed tuberculosis of the spleen, liver and lungs, and arteriosclerotic renal changes.

Examination of the esophagus revealed that the dilatation began abruptly 2 cm. above the junction of the gastric and the esophageal mucosa. The sac, which had a circumference of 7 or 8 cm. throughout most of its length, extended to the cricoid cartilage, which was 26 cm. above the cardia. The lower part of the sac had thick muscular walls while the upper 8 cm. of the sac showed thinning of both the mucosal and the muscular layer. In the lower part of the sac there were numerous thickened plaques in the epithelium, which produced a pebbled-leather appearance (fig. 7). In the lowest 5 cm. of the esophagus there was ulceration between the islands of epithelial thickening. Just above the neck of the cardiospasm one such ulcer had penetrated almost to the adventitia. There was no diverticulum or evidence of kinking or twisting of the esophagus.

Microscopic study showed a general thickening of the esophageal epithelium. Between the plaques of thickened epithelium in the lower part of the esophagus there was acute necrotic and ulcerative inflammation, with many polymorphonuclear leukocytes, which involved the mucosa and submucosa. The muscular layer was thickened in the lower portion of the sac. There was thinning of the circular muscle in the upper part of the sac, with vacuolar degeneration of the muscle fibers but no fibrosis. Circular elastic fibers were relatively more

prominent in the upper part of the sac. The ganglion cells generally had disappeared; only two were seen in eight segments of the myenteric plexus. Their place was taken by some proliferation of the supporting cells. No sections of the vagus nerve could be obtained.

CASE 9.—A woman aged 39 had suffered from epigastric pain, vomiting and dysphagia for nineteen years. She had undergone frequent dilation for cardiospasm from 1914 to 1918. A roentgenogram, which was made in 1918, showed both a dilated esophagus and a duodenal ulcer. She returned to the clinic and

Fig. 7.—Esophagus (case 8) showing the plaques of epithelial thickening mingled with ulceration just above the cardia.

underwent further dilations on Jan. 3, 1925, Nov. 5, 1925, and March 31, 1926. The last operation was followed by epigastric pain and bloody emesis. The following day, dulness was noted at the base of the lungs, especially on the left side. During the next few days five aspirations were performed for empyema of the left pleura, and from 300 to 1,000 cc. of fluid was removed at each aspiration. The patient died on April 10, 1926.

Necropsy revealed that rupture of the esophagus had been followed by mediastinitis and empyema on the left side, which had collapsed the lung completely. There also were fibrinous pleuritis at the base of the right lung, a healed duodenal

ulcer, fatty changes in the myocardium and liver, infarcts in the spleen and left kidney and gas bubbles and hemolysis in the submucosa of the colon, from which Clostridium Welchii was isolated.

Examination of the specimen showed that the neck at the cardia, which had a circumference of 3.9 cm., was dilated gradually to a relatively small sac, 16 cm. in length and 5.5 cm. in circumference. Beginning 2 cm. above the mucosal junction and extending upward 5.2 cm. was a complete tear through the esophagus. In the middle of the sac the epithelium was dark and lusterless and had the appearance of infarction. There was no diverticulum, scarring, evidence of a twist or kink or hypertrophy of the sphincter or oblique muscle at the cardia.

Microscopically the epithelium showed merely a hyperplastic downward growth of the basal layers, except in regions (as around the rupture or in the middle of the sac) in which the epithelium was lost in acute esophagitis. Sections from the borders of the rupture demonstrated that both mucosa and musculature originally had been normal where the tear occurred. The edges of the tear were covered with pseudomembranous inflammation. Above the rupture, in the middle of the sac, the layers of the esophagus were completely disorganized. The whole wall was a mass of necrotic tissue, hemorrhage and inflammation. Even the myenteric plexus could not be recognized definitely enough to permit the ganglion cells to be counted. Outside the infarcted region the muscular layer appeared normal, except for a slight increase in the fibrous tissue and circular elastic tissue near the cardia. Six segments of myenteric plexus from parts of the esophagus unaffected by the acute infarction showed only one ganglion cell. The ganglions showed some increase in the number of nuclei of the supporting cells. No sections of the vagus nerve could be obtained.

Case 10.—A man aged 31 had suffered a sudden onset of epigastric pain and regurgitation four years before he came to the clinic. The gallbladder and appendix had been removed elsewhere, without relief. Since that time there had been increasing dysphagia, regurgitation and loss of weight. On his trip to the clinic he had become mentally confused. Shortly after his arrival he became acutely maniacal. Examination was impossible. He was sent to the state hospital, where he died seven days later.

At necropsy a diagnosis was made of dilatation of the esophagus, emaciation, toxic psychosis (possibly the result of hunger and dehydration), exhaustion, edema and congestion of the brain and old healed tuberculosis of the lungs and lymph nodes.

Examination showed that the esophagus, which was normal in size at its lower extremity, was dilated gradually to a fusiform sac with a maximal circumference of 11 cm. at a point 10 cm. from the cardia. The epithelium was generally thickened. In the lower part of the sac were several small papillomatous protrusions of the mucous membrane, which averaged 2 mm. in diameter. The muscular layer of the esophagus was relatively thin. There was no ulceration, diverticulum or evidence of a twist or kink in the esophagus or of hypertrophy of the oblique muscle.

The epithelium was normal microscopically, except for some thickening. One section near the cardia, however, passed through the scar of a healed ulcer. This old ulcer, which was not recognized grossly, had once extended down to the circular muscle. The muscular layer appeared normal and did not exhibit any fibrosis. The number of circular elastic fibers was markedly increased in the sac. The ganglion cells had mostly disappeared from the myenteric plexus, only three cells being seen in fifteen segments. The ganglion cells had been replaced

by a proliferation of supporting cells, which frequently appeared in the form of whorls, which I have labeled glomeruloids. Sections of the vagus nerve appeared normal.

CASE 11.—A man aged 62 first came to the clinic in 1921, because of stomach trouble, which had been present for three years. A diagnosis of cardiospasm was made and dilation relieved the symptoms. He returned frequently between 1923 and 1929, because of chronic arthritis. From March 21 to April 25, 1929, several casts were applied to his knees for wedging. There was no manipulation of the joints, however. On April 29 the patient suddenly fell unconscious in a convulsion. He revived for a few minutes and then collapsed and died.

Necropsy did not solve satisfactorily the question of the cause of death. The observations included chronic pulmonary tuberculosis, healed tuberculosis of the spleen and liver, chronic arthritis and moderate arteriosclerosis. The brain was normal.

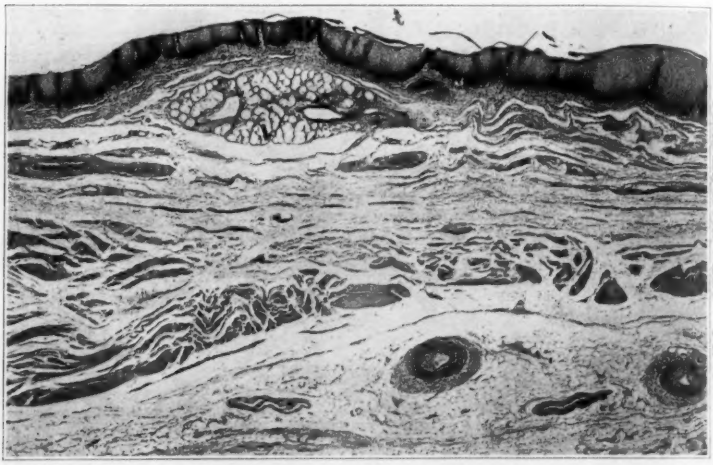

Fig. 8.—Section of the esophagus, × 16, near the cardia (case 11). At the extreme upper right is an island of thickened epithelium. That this thickness is not an artefact resulting from oblique cutting is shown by the fact that the papillae are cut in the direction of their axes. In the upper center is an esophageal gland. Below and to the right of it the muscular wall of the esophagus consists of longitudinal fibers only; the circular muscle apparently has been ruptured in the course of operative dilation.

The lowest 4 cm. of the esophagus, which constituted the neck of the dilated esophagus, was of normal size. Above this was a sac which was dilated to a circumference of 8.5 cm. The mucosa presented numerous islands of thickened epithelium. Twelve centimeters from the cardia was a diverticulum 0.6 cm. deep and 1.6 cm. across its mouth. There was no scarred lymph node attached to the fundus of the diverticulum. On the outer surface of the sac was one strand of longitudinal muscle which was greatly thickened.

Microscopically the epithelium showed numerous islands of thickening and elongated papillae (fig. 8). Occasional polymorphonuclear leukocytes were seen

in the thickened epithelium. There was no ulceration. At the cardia and in the neck of the cardiospasm the circular muscle had the appearance of having been pulled apart. It was atrophic; the strands were separated, and some sections did not reveal any circular muscle at all. I have mentioned this as a late appearance following successful dilation. In the sac the muscular layers were generally normal, except that the thickened strand of longitudinal muscle, which was mentioned in the gross description, disclosed considerable vacuolar degeneration of the muscle cells. Special staining revealed that the vacuoles did not contain fat. In the walls of the sac the capillaries and small veins were greatly dilated. The amount of circular elastic tissue was relatively increased in the sac. The diverticulum had the appearance of a herniation of the mucosa through the muscular wall of the esophagus. The muscularis mucosae was normal throughout the diverticulum, but the circular muscle was thinned almost to extinction, and the strands of the longitudinal muscle were pushed to the sides. Ganglion cells generally had disappeared throughout the esophagus; only seven were seen in sixteen measured segments of the myenteric plexus. There was little proliferative reaction in the ganglions. Sections of the vagus nerve were normal.

Case 12.—A woman aged 60 had complained of "gas on the stomach" for two years. For seven months before she came to the clinic there had been progressive dysphagia. Administration of belladonna had given transient relief, but the patient had lost 25 pounds (11.3 Kg.). When she came to the clinic she was pale, weak and emaciated. She was told to swallow thread for a guide for dilation. At noon on the first day she became dyspneic after eating. A few physical signs were discovered over the lower lobe of the left lung. Despite oxygen therapy, she died the same evening (Nov. 8, 1932).

Necropsy revealed edema of the lungs and a limited beginning pneumonia. There was a pedunculated lipoma on the outside of the stomach, near the cardia. A mucocele of the appendix, one gallstone, granular cystitis, moderate arteriosclerosis and healed pulmonary tuberculosis were also present.

A specimen of the esophagus showed more dilatation and more thinning of the wall than were present in any case that I previously had studied (fig. 9). The neck, or undilated portion, of the esophagus extended upward 1.5 cm. from the mucosal junction with the stomach. Above this was a sac which measured 25 cm. in length and 16 cm. in its greatest circumference. The thinning of the wall involved both the muscular and the mucosal layer. A few varicose veins were seen in the submucosa. There was no diverticulum or ulceration or any evidence of a thickened sphincter, hypertrophied oblique muscle or kink in the esophagus at the cardia. The stomach likewise was considerably dilated.

Microscopic examination showed that the epithelium was generally thinned, except for a few islands of localized thickening at the cardia. No ulceration was present. The muscular layers were thinned throughout but more so in the sac than in the neck of the cardiospasm. There was a slight increase in the amount of circular elastic fibers in the neck, but a general thinning of all elastic fibers was noted in the sac. The number of ganglion cells in the myenteric plexus was reduced; only twelve cells were seen in twelve measured segments. The complete vagus plexus, which was examined with many sections and stains, was entirely normal.

Case 13.—A man aged 69 died at the clinic with uremic symptoms on May 22, 1934. At no time had he complained of dysphagia. When his wife was questioned in the light of the postmortem observations, however, she recalled that in his youth the patient had suffered great difficulty in swallowing. He had

vomited with great ease and had found it necessary to sleep with a towel on his pillow and a rug beside his bed on account of regurgitation at night. These symptoms had not troubled him for many years.

Besides the dilated esophagus, necropsy revealed carcinoma of the bladder, which had metastasized to the ureters, liver, lung and lymph nodes; pyelonephritis; chronic tuberculosis of the hilus, lymph nodes and spleen, and hypertrophy of the heart.

The relationship between the cardia and the diaphragm was examined in situ, and it was observed that there was room in the esophageal hiatus to slip two fingers

Fig. 9.—The esophagus and stomach (case 12) before being opened.

between the esophagus and diaphragm. A plaster cast was made of the stomach and esophagus before these organs were opened. The cast was not absolutely continuous between the two organs because the lower end of the cardia was partially occluded by a wad of vegetable fibers. The esophagus was not only greatly dilated but also somewhat stretched lengthwise. As a consequence, there was some bending of the esophagus, but obviously there was not enough kinking to produce obstruction, as the cast demonstrated. Beginning at the cardia, a neck, or undilated portion of the esophagus, extended upward for a distance of 4.5 cm. In this portion the muscular walls were thick, and the mucosa was folded longitudinally. The esophagus then curved to the right and gradually widened into a sac which was 14 cm. long and 16 cm. in circumference. The mucosal and muscular

walls of the sac were thinned. The epithelium presented numerous ulcers, which were 1 or 2 mm. in diameter. About 2.5 cm. above the upper end of the neck was a diverticulum 0.7 cm. in depth. Its mouth measured 0.6 cm. in its vertical and 1.5 cm. in its horizontal diameter. At the upper end of the sac, opposite the

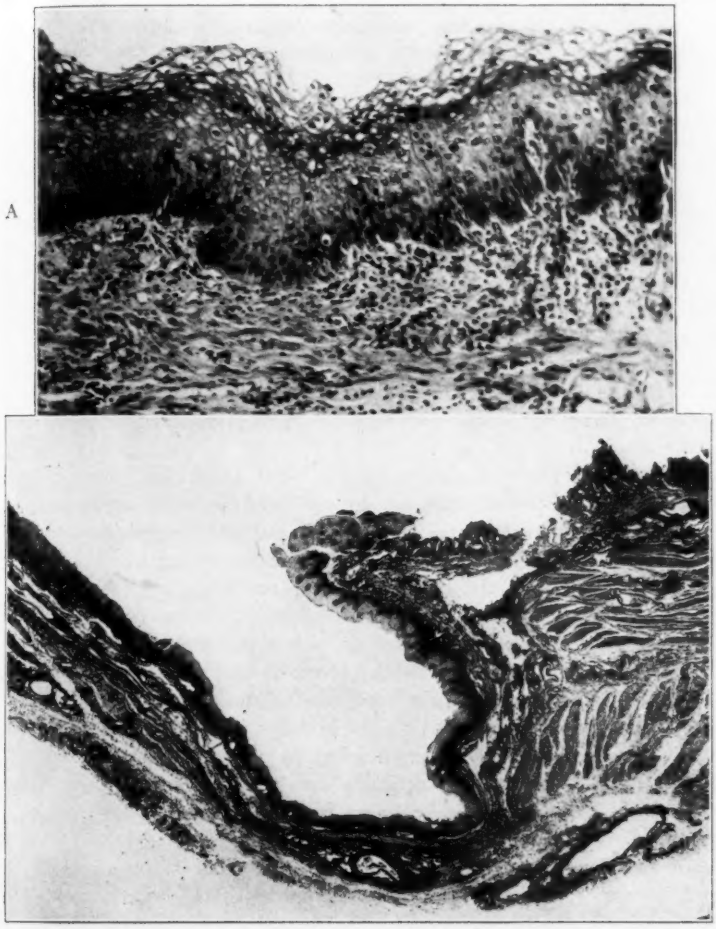

Fig. 10.—*A*, the epithelium of the esophagus (case 13) showing pathologic cornification, × 115. *B*, a diverticulum of the esophagus (case 13; × 10). On the right may be seen the strands of circular and longitudinal muscle, apparently pushed aside by the pouch, which is lined only with muscularis mucosae.

bifurcation of the trachea, was another undilated portion of the esophagus, which had thick muscular walls. I shall speak of it as the upper neck. It curved to

the left and had a length of 4 cm. and a circumference, when opened, of 7 cm. Above this was another thin-walled sac, which reached to the cricoid cartilage. It was 7.5 cm. long and 10.5 cm. in circumference.

Microscopically the epithelium was thickened throughout. Near the cardia it was somewhat edematous, and above this point it presented beginning cornification of the mucous membrane type (fig. 10 *A*). In the lower neck the muscular layers were much thickened but otherwise were normal and free from fibrosis. In the lower sac there was not only much thinning but also extensive fibrosis of the muscle. In the upper neck the muscle was normal, but much thickened; the circular muscle had a thickness of 6 mm. In the upper sac the muscular layers were thin but otherwise normal. Here, the muscle fibers were largely striated. The elastic fibers were relatively increased in number in the upper and lower necks and at the sites of fibrosis. In the latter situations circular fibers predominated. The wall of the diverticulum resembled that in the eleventh case, in that the longitudinal fibers appeared to be pushed apart, the circular fibers were thinned to extinction and only the muscularis mucosae was present in the fundus of the diverticulum (fig. 10 *B*). Ganglion cells had disappeared throughout the esophagus; no cells were seen in nineteen measured segments of the myenteric plexus. Practically no proliferative changes were evident in the ganglions. Sections of the vagus nerve were normal.

COMMENT

The details of the clinical findings in these cases are shown in table 2. The conclusions which may be drawn from them have no small importance.

In all cases the dilated portion of the esophagus, or sac, was separated from the stomach by an undilated segment of esophagus, which I have labeled the neck. The neck varied in length between 1.5 and 4.5 cm. In no case was there organic narrowing of the neck or scarring in or around it. Accordingly, one may lay the ghost of Mosher's "fibrosis of the terminal esophagus." In no case was there evidence of a thickened sphincter or of a hypertrophic oblique muscle of the stomach. "Kinking of the terminal esophagus" was certainly absent in all cases of early moderate dilatation. Kinking of the esophagus can evidently occur only in cases of very old cardiospasm in which there has been lengthening as well as dilatation of the esophagus. Accordingly, it probably can be eliminated as an etiologic factor. No evidence could be found for compression of the esophagus by spasm of the diaphragm. The absence of hepatomegaly and of any pathologic condition in the liver in this and other series of cases of cardiospasm speaks strongly against "pressure of the liver tunnel" as a cause of the dysphagia. Finally, the theory which invokes "the pressure of the lung tips" can be eliminated by an appeal to simple physics—the lungs are elastic and do not press against but tend to pull away from the parieties.

In ten of the thirteen cases in which adequate sections could be obtained the vagus nerve was entirely normal. In every case, however, there was a striking loss or complete absence of ganglion cells from the

myenteric plexus. Only seventy-four cells were seen in a total of 233 segments of the myenteric plexus, which were 1 cm. in length. This loss was frequently accompanied with a proliferation of the supporting cells of the ganglions. Sometimes there was a picture which I have interpreted as a mass of new proliferative supporting cells filling the old capsule of an extinct ganglion cell. I have termed this appearance a glomeruloid. Sometimes there was actual inflammation in and about the ganglions. In some cases there was nothing to be seen except simple absence of ganglion cells from the ganglions.

TABLE 2.—*Data for Thirteen Cases of Cardiospasm*

Case	Sex	Age, Years	Duration of Symptoms, Years	Operative Dilation	Rupture of Esophagus	Cause of Death	Diverticulum of Esophagus	Maximal Circumference of Sac (Fixed), Cm.		Thickness of Muscle in Sac
								Peptic Ulcer		
1	M	53	5	+	0	Unknown (cardiac?)	0	Gastric	8	Normal
2	F	29	2	+	+	Cellulitis of neck	0	0	5.4	Increased
3	F	39	17	+	+	Empyema on left	0	0	?	Increased
4	M	17	11+	0	0	Unknown	0	0	8	Increased
5	F	66	3	+	+	Bilateral empyema	0	0	8	Increased
6	F	8	3	0	0	Inanition	0	0	7.5	Increased
7	M	58	20	+	+	Empyema on left	0	0	5.6	Increased
8	M	50	2	0	0	Inanition and pneumonia	0	Healed duodenal ulcer	7.5	Increased
9	F	39	19	+	+	Empyema on left	0	Healed duodenal ulcer	5.5	Decreased
10	M	31	4	0	0	Toxic psychosis	0	0	9	Normal
11	M	62	11	+	0	Unknown	+	0	8.6	Irregular
12	F	60	2	0	0	Unknown (edema of lungs?)	0	0	16	Decreased
13	M	69	30+	0	0	Carcinoma of bladder	+	0	16	Decreased

In may be argued that the loss of ganglion cells is secondary to pressure in the dilated sac. It is to be pointed out, however, that the loss of ganglion cells is equally great in the undilated neck at the cardia. Furthermore, it should be pointed out that in most of these cases the circumference of the sac was only about twice the circumference of the normal esophagus. Accordingly, the increased mean distance between ganglion cells can account for a reduction of only about 50 per cent in the number of cells in the sac.

My results are compatible with the theory of Hurst,[71] namely, that cardiospasm, or achalasia of the cardia, is primarily a disease of the myenteric plexus. Hurst expressed the opinion that with the destruction of the myenteric plexus the sympathetic fibers to the terminal portion of the esophagus are allowed to act unopposed. As a result, the terminal portion of the esophagus does not relax normally with the swallowing reflex, and dysphagia results.

The varying anatomic pictures in these thirteen cases can best be explained by introducing the conception of "compensated" and "decompensated" cardiospasm. In early and moderate cardiospasm the esophagus responds to the obstruction in a characteristic fashion. It dilates only slightly. Instead, the muscular walls, and especially the circular muscle, are greatly thickened. The thickness of the circular elastic fibers also is relatively increased in response to the increased pressure within the esophagus. The epithelium also is thickened uniformly but does not become ulcerated. Case 2 furnishes an excellent example of such a compensated cardiospasm.

If the long-continued and severe pressure from within, however, overcomes the resistance of the esophagus to dilatation, certain other changes occur. The esophagus becomes prodigiously dilated and also stretched lengthwise, so that bends and kinks may occur. The muscle, instead of being thicker than normal, is thinned. The muscular fibers in the sac may show vacuolar changes or even extensive fibrosis (case 13). Also, the elastic tissue of the esophagus is thinned out. There may be dilatation of the capillary venules as a result of obstruction to the venous return. The mucosa may herniate through the muscular wall in the form of a diverticulum (cases 11 and 13). The epithelium may show beginning cornification or plaques of great thickening or ulceration. In case 13 is presented a typical picture of decompensated cardiospasm. Most of the anatomic features in these thirteen cases can be regarded as representing various stages of compensation. The chronically infected esophagus in case 6 and the completely atonic esophagus in case 12 are somewhat atypical but may fit into the same scheme.

It is now necessary to consider the effect of operative dilation on the cardia. In most of these cases rupture of the esophagus complicated the picture. In case 11, however, operative dilation of the cardia, years previously, produced complete relief of symptoms. In this case the fibers of the circular muscle in the neck of the cardiospasm were pulled apart in a way that points to an old submucous rupture of the circular muscle. This same frayed appearance of the circular muscle was present after recent dilation in case 3.

71. Hurst, A. F.: (*a*) The Treatment of Achalasia of the Cardia (So-Called "Cardiospasm"), Lancet **1**:618-619 (March 19) 1927; (*b*) Some Disorders of the Esophagus, J. A. M. A. **102**:582-587 (Feb. 24) 1934.

In case a rupture through the wall of the esophagus is produced by operation, certain characteristic observations are made. In case 2, in which dilation was performed elsewhere, the esophagus had been punctured high in the cervical region, apparently with some pointed instrument. Cases 3, 5, 7 and 9, however, in which the rupture followed the use of the Plummer dilator, were markedly similar. The tear was always longitudinal. It was always through a normal mucous membrane and muscular wall. In three cases it produced only empyema on the left side, and in the one case, in which bilateral empyema was produced, the rupture was on the left side of the esophagus. The tear was either entirely above the juncture with the mucous membrane of the stomach (in three cases) or almost entirely above the juncture (in one case). The rupture was always followed by a rapidly spreading inflammatory reaction of great violence.

One more point remains to be considered. In cases 1, 4, 11 and 12 death occurred suddenly and could not be explained satisfactorily by the postmortem observations. I should not care to defend the thesis that the sac in a case of cardiospasm may exert such pressure on the mediastinal structures as to be the cause of sudden death; yet this possibility is worthy of consideration.

Progress in Internal Medicine

DISEASES OF METABOLISM AND NUTRITION

REVIEW OF CERTAIN RECENT CONTRIBUTIONS

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II. NUTRITION

By Dr. Wilbur

Although the symptomatic and, to some extent, the pathologic results which accompany states of marked deprivation of vitamins have been largely described, great interest has been shown in the past year in the early alterations in normal physiologic processes which occur before these gross pathologic changes have become manifest. In fact, chief interest in the field of nutrition is at present directed toward studies of the metabolic influences of the various vitamins. Of particular interest to clinicians have been methods of recognition and treatment of states of moderate and mild vitamin deficiency, the effect of abnormalities in gastro-intestinal function in the production or conditioning of disease due to vitamin deficiency, studies of the metabolism of vitamin C and, lastly, studies of the physiologic properties of the vitamin B complex, elucidation of the components of which has advanced steadily.

VITAMIN A

The daily requirement of vitamin A is still unknown. Indeed, it probably will be many years before the requirement of vitamin A or of any of the other vitamins can be clearly established. The difficulty in expressing in exact figures the requirement of any vitamin is realized when one considers the influences of absorption, storage and destruction and the variability in minimal and optimal requirement. Perhaps eventually the quantitative requirement will be stated, as it now is for protein, to lie between certain minimal and optimal levels. This tendency has already received expression in the report of a cooperative committee appointed by the Council on Pharmacy and Chemistry and the Committee (now Council) on Foods,[1] both of the American Medical Association.

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The section on "Diseases of Metabolism" was published in the February issue of this journal.

1. The Status of Certain Questions Concerning Vitamins, report of the Council on Pharmacy and Chemistry, J. A. M. A. **106**:1732-1735 (May 16) 1936.

This committee has recommended for approval for lay advertising any cod liver oil or preparation containing vitamin A if the prescribed daily dose provides at least 6,250 and not more than 10,000 U. S. P. units of vitamin A. This is the vitamin content provided by 2 teaspoonfuls of cod liver oil, which meets the standard given in "New and Nonofficial Remedies" (1936). The committee noted a lack of data on the basis of which to determine the dose of vitamin A for adults, although Harris [2] placed the minimal requirement at about 1,000 U. S. P. units daily. The requirement of children per kilogram of body weight is greater than that of adults, because of the processes of growth.

By healthy subjects vitamin A and its precursor, the yellow pigment carotene, are absorbed without difficulty. Evidence gradually has accumulated to show that absorption of vitamin A and carotene may be influenced by a variety of pathologic and perhaps physiologic processes and that under many circumstances the absorption of carotene is more often interfered with than is that of the vitamin itself. It has been suggested that whenever interference with the digestion or absorption of fat occurs, there may be failure in absorption of vitamin A or carotene. In this respect interesting studies have been reported in the past year on the rôle of bile in the utilization of vitamin A. The indispensability of bile in absorption of lipids and the fat-soluble character of the vitamin suggest that, in the absence of bile, there might be serious interference with absorption of vitamin A. However, studies of Schmidt and his associates [3] have indicated that absorption of vitamin A of cod liver oil from the gastro-intestinal tract of the rat does occur in the absence of bile, as indicated by studies of vaginal smears as a criterion of deficiency. In contrast, it was found that the rat suffering from deficiency of vitamin A did not respond to oral administration of alpha carotene and beta carotene in the absence of bile. Response occurred, however, when the carotene was administered subcutaneously by injection or when it was administered orally, together with bile acids. In a somewhat related study Altschule [4] recorded his observations of 11 infants in whom the bile duct was observed post mortem to be congenitally atretic. All the infants had received an adequate diet and had failed to present clinical evidence of vitamin A deficiency. However, in tissues of 6 of the 11 were microscopic changes similar to those

2. Harris, L. J.: A Programme for Nutrition Surveys, Lancet **1**:966-968 (April 25) 1936.

3. Greaves, J. D., and Schmidt, C. L. A.: On the Absorption and Utilization of Carotene and Vitamin A in Choledochocolonostomized Vitamin A Deficient Rats, Am. J. Physiol. **111**:492-501 (April) 1935. Schmidt, W., and Schmidt, C. L. A.: The Relation of Bile to the Intestinal Absorption of Vitamin A in the Rat, Univ. California Publ., Physiol. **7**:211-221, 1930.

4. Altschule, M. D.: Vitamin A Deficiency in Spite of Adequate Diet in Congenital Atresia of the Bile Ducts and Jaundice, Arch. Path. **20**:845-856 (Dec.) 1935.

Wolbach and Howe [5] have described in vitamin A deficiency. Altschule said he considered this as evidence that vitamin A had not been absorbed in adequate amounts because of the absence of bile. Consideration must also be given in this connection to the relation of the damaged liver to storage and metabolism of vitamin A.

That infections may influence intestinal function, and particularly absorption, has long been recognized. Heymann's [6] interesting studies disclosed that 70 per cent of ingested carotene was absorbed by normal infants, whereas if the infants harbored infection of any type, only 36 per cent was absorbed. Heymann expressed the belief that low absorption is not attributable to fever only, since the effect persisted for two weeks beyond the duration of the fever. Heymann could find no evidence that it was attributable to inhibition of absorption of fat and ascribed it to an unknown toxic effect. In the presence of celiac disease, in which absorption of fat is greatly interfered with, vitamin A deficiency has been reported by Friderichsen,[7] even though vitamin A was given in sweet milk. When the infant under his observation was given mother's milk, immediate improvement resulted. Heymann also has studied a patient with celiac disease who showed complete lack of absorption of vitamin A. Evidence which is interpreted as indicating interference with absorption of vitamin A in pregnancy has been reported by Edmund and Clemmesen.[8] Thirteen of 20 pregnant women presented night blindness which was relieved in from seven to ten minutes by intramuscular injection of a preparation containing 15,000 U. S. P. units of vitamin A in each cubic centimeter.

Further evidence of the importance of the liver in metabolism of vitamin A is demonstrated by the studies of Heymann [9] and of Ralli, Pariente, Brandaleone and Davidson.[10] Heymann reported that after cessation of administration of carotene in oil, diabetic patients failed

5. Wolbach, S. B., and Howe, P. R.: Tissue Changes Following Deprivation of Fat-Soluble A Vitamin, J. Exper. Med. **42**:753-777 (Dec.) 1925.

6. Heymann, W.: Absorption of Carotene, Am. J. Dis. Child. **51**:273-283 (Feb.) 1936.

7. Friderichsen, C.: Quantitative Investigations of the Resorption of A Vitamin in a Case of Coeliakie: Studies of Hypovitaminosis-A, Acta pædiat. **18**: 377-391, 1936.

8. Edmund, C., and Clemmesen, S.: On Parenteral A Vitamin Treatment of Dysaptatio (Nyctalo-Hemeralopia) in Some Pregnant Women, Acta med. Scandinav. **89**:69-92, 1936.

9. Heymann, Walter: Carotenemia in Diabetes, J. A. M. A. **106**:2050-2052 (June 13) 1936.

10. Ralli, Elaine P.; Pariente, A. C.; Brandaleone, H., and Davidson, S.: Effects of Carotene and Vitamin A on Patients with Diabetes Mellitus: III. The Effect of the Daily Administration of Carotene on the Blood Carotene of Normal and Diabetic Individuals, J. A. M. A. **106**:1975-1978 (June 6) 1936.

to show the normal decline in the carotene content of the serum; the concentration remained elevated or even increased for from ten to fourteen days after administration had been discontinued. Ralli and his associates reported that the ability of the liver of diabetic patients to convert carotene to vitamin A is diminished and that this leads to increased concentration of carotene in the liver, which in turn interferes with the absorption of carotene from the blood. The evidence indicates that the carotenemia of diabetic patients is not attributable solely to the large carotene content of the diet.

It has long been recognized that vitamin A deficiency is manifested chiefly by an effect on epithelial tissues. It was suggested by Mellanby [11] in 1934 that the primary effect of vitamin A deficiency is on nerve tissues and that the epithelial changes may be secondary, attributable to interference with or loss of trophic influences. Although certain changes in the nervous system of animals deprived of vitamin A have been described, such as those recently described by Zimmerman and Cowgill,[12] the conception of Mellanby remains unproved. In an attempt to support this hypothesis by experimental means, King [13] cut the inferior dental nerves of dogs. This accelerated the rate of growth of the teeth but failed to produce defects such as those observed in the teeth and gums of dogs suffering from vitamin A deficiency. That the results he obtained were attributable to damage of the vasomotor fibers is indicated, since the changes observed were reproduced by section of the cervical sympathetic nerve.

Further attempts to find practical value in the relation of vitamin A to epithelial tissues have led to the use of the vitamin to aid in the healing of wounds and in the treatment of epithelial lesions. Most of the reports of this work have appeared in the foreign literature. Proto [14] and Sandor [15] have reported favorable results. Proto stated that in experimental wounds of rabbits local applications of vitamin A greatly and favorably influenced healing. Concerning the treatment in man of large superficial wounds or of areas from which skin had been excised, Sandor reported favorably on the effect of an ointment or oil

11. Mellanby, E.: Xerophthalmia, Trigeminal Degeneration and Vitamin A Deficiency, J. Path. & Bact. **38**:391-407 (May) 1934.

12. Zimmerman, H. M., and Cowgill, G. R.: Lesions of the Nervous System in Vitamin Deficiency: IV. The Effect of Carotene in the Treatment of Nervous Disorders in Rats Fed a Diet Low in Vitamin A, J. Nutrition **11**:411-423 (May) 1936.

13. King, J. D.: Dietary Deficiency, Nerve Lesions and the Dental Tissues, J. Physiol. **88**:62-76 (Oct.) 1936.

14. Proto, M.: Action of Vitamins on Healing of Wounds, Ann. ital. di chir. **15**:1-174 (Jan.-Feb.) 1936; abstr., J. A. M. A. **107**:627 (Aug. 22) 1936.

15. Sandor, Stephan: Vitamin A in the Local Treatment of Wounds, Lancet **2**:738-740 (Sept. 26) 1936.

containing 2,000 U. S. P. units of vitamin A in each cubic centimeter. Of considerable interest is the report of Lustig and Wachtel[16] on experiments with vitamin A in treatment of cutaneous epitheliomas and mammary carcinomas. After using a preparation containing 40,000 biologic units of vitamin A in each cubic centimeter applied as compresses and injection subcutaneously along with a colloidal copper preparation, these investigators reported that the involved area became smaller. New epithelium grew in from the periphery, and the bases of the ulcers became clear. No effect was noted on distant metastatic growths. While Lustig and Wachtel admitted that the treatment was palliative, since cures had not occurred, nevertheless they said they were inclined to continue their study and felt that perhaps the use of vitamin A would prove an adjuvant in the treatment of the lesions. Failure of massive doses of carotene in oil administered to rats to influence implanted sarcomatous tumors has been reported by Sure, Buchanan and Thatcher.[17]

The relation of vitamin A to genito-urinary function has received further study in the past year. Higgins[18] has continued his studies on urinary calculi associated with vitamin A deficiency. He reported 35 cases in which stones had undergone solution and stated that in his experience since 1932 the incidence of recurring stones following operation has been reduced from 16.4 to 4.7 per cent. Lazarus and Rosenthal,[19] however, have failed to be convinced of the efficacy of the high vitamin acid ash diet, either as a means of dissolving stones or as an absolutely certain means of preventing recurrences. They were unable to explain their failure to reproduce Higgins' results, although failure to treat patients over a sufficiently long period of time may have been a factor. In this connection the report of the cooperative committee,[1] previously noted, is of interest, for it is stated that "there is at the present time inadequate evidence to warrant the claim that the ingestion of sufficient vitamin A will prevent the formation of renal calculi in man."

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16. Lustig, B., and Wachtel, H.: Therapeutic Experiments with Vitamin A in Cancer, Ztschr. f. Krebsforsch. **44**:53-58, 1936; abstr., J. A. M. A. **107**: 1261 (Oct. 10) 1936.

17. Sure, B.; Buchanan, K. S., and Thatcher, H. S.: Vitamin A and Carcinogenesis, Am. J. Cancer **27**:84-86 (May) 1936.

18. Higgins, C. C.: Urinary Lithiasis: Experimental Production and Solution with Clinical Application and End-Results, J. Urol. **36**:168-177 (Aug.) 1936.

19. Lazarus, J. A., and Rosenthal, A. A.: Renal Lithiasis—A Résumé of Its Present Status and a Preliminary Report on the Vitamin "A" Acid Ash Diet Based upon One Hundred and Twenty-One Private Cases, Urol. & Cutan. Rev. **40**:1-8 (Jan.) 1936.

The effect of deprivation of vitamin A on the vaginal mucosa has long been recognized, and the effect on the vaginal mucosa of the rat has been used as a measure of vitamin A sufficiency or insufficiency. Coward, Cambden and Lee [20] have reported that as a means of quantitative estimation of vitamin A, the method appears to be somewhat less accurate than determination of increase in weight in three weeks of female rats which have been given daily doses of vitamin A after they have ceased to grow on a diet deficient in that factor. Simpson and Mason [21] have studied the relation of senile vaginitis in human beings to vitamin A deficiency. In 30 cases, in many of which the subjects had been receiving an inadequate diet, an increased oral intake of vitamin A, in cod liver oil or halibut liver oil, proved to be an unusually effective method of producing rapid relief of symptoms and of gross and histologic repair of the vaginal lining.

The relation of vitamin A to resistance to infection has long been a matter of debate. The vitamin has certainly not been shown to be specific in the prevention of colds, influenza and such infections, nor has it been demonstrated that ingestion of vitamin A in amounts far in excess of those readily obtained from a properly selected diet is an aid in preventing infections. Mackay and her associates [22] have contributed an interesting but not conclusive study in this respect on the therapeutic value of vitamins A and D in measles. In a group of 697 children less than 13 years of age these investigators failed to find any favorable effect on the fatality rate or on the incidence of pneumonia, otorrhea and all other complications, including cutaneous lesions, while the patients were in the hospital. Moreover, the duration of pyrexia or length of stay in the hospital was not affected. To children of one group was given 3,000 U. S. P. units of vitamin D daily, to those of another group this dose of vitamin D plus the vitamin A equivalent of 22.5 cc. of cod liver oil daily and to those of a third group no vitamin supplements. The negative results may have been attributable to the short time of administration of the vitamins or to the fact that treatment was started too late (81 per cent about the fourth day or later in the disease).

Recognition and Frequency of States of Vitamin A Deficiency.—Recognition of states of marked deprivation of vitamin A is not difficult

20. Coward, Katharine H.; Cambden, Marjorie R., and Lee, Eva M.: The Determination of Vitamin A by Means of Its Influence on the Vaginal Contents of the Rat, Biochem. J. **29**:2736-2741, 1935.

21. Simpson, J. W., and Mason, K. E.: A New Concept of Senile Vaginitis, Am. J. Obst. & Gynec. **32**:125-128 (July) 1936.

22. Mackay, Helen M. M.; Linford, Hilda M.; Mitman, Maurice, and Wild, Mary H.: The Therapeutic Value of Vitamins A and D in Measles, Arch. Dis. Childhood **11**:127-142 (June) 1936.

if one keeps in mind lesions involving the eyes and the skin. Excellent summaries of the manifestations of vitamin A deficiency have been made by Sweet and K'ang [23] and by Loewenthal.[24] It seems obvious that these conditions of marked deficiency are rare in the United States, and consequently most attention has been directed toward the much more important problems of the means of recognizing states of mild deficiency. In this connection the work of Jeans and Zentmire,[25] first reported in 1934, has been outstanding, and further confirmation of the value of their photometric method of recording impaired visual adaptability to darkness has been reported by them as well as by Frandsen,[26] in Denmark. This or some similar simple method seems to be of much value in clinical work, although as yet the limitations of such methods as tests of vitamin A deficiency have not been determined.

Youmans,[27] in an excellent summary of methods of recognizing vitamin deficiencies in practice, has emphasized the types of ocular and cutaneous symptoms, signs and tests which may be of value in states of vitamin A deficiency. Ocular symptoms, including asthenopia, poor vision, photophobia, Bitot's spots, conjunctival complaints, dryness and granular appearance of the bulbar conjunctiva when the eyelids are held open for a few minutes, are all signs that arouse suspicion but are inconclusive. Smears of conjunctival or nasal scrapings containing keratotic cells have been described by Blackfan and Wolbach,[28] and Sweet and Klang have given further objective evidence. Further confirmation lies in the use of some test, such as the test of adaptability to darkness, of Jeans and Zentmire. Friderichsen has described a method which may overcome some of the objections to the test of Jeans and Zentmire. This depends entirely on objective changes; the observer measures the faintest light which will provoke an oculomotor reflex. Cutaneous evidence of vitamin A deficiency, well described by Frazier

23. Sweet, L. K., and K'ang, H. J.: Clinical and Anatomic Study of Avitaminosis A Among the Chinese, Am. J. Dis. Child. **50**:699-734 (Sept.) 1935.

24. Lowenthal, L. J. A.: The Manifestations of Vitamin A Deficiency in Man, Ann. Trop. Med. **29**:407-413 (Dec. 18) 1935.

25. Jeans, P. C., and Zentmire, Zelma: A Clinical Method for Determining Moderate Degrees of Vitamin A Deficiency, J. A. M. A. **102**:892-894 (March 24) 1934.

26 Frandsen, Helga: Hemeralopia as an Early Criterion of A-Avitaminosis and Clinical Symptoms and Treatment of This Disease, Acta ophth., supp. 4, 1935, p. 7-160.

27. Youmans, J. B.: The Present Status of Vitamin Deficiencies in Practice, J. A. M. A. **108**:15-20 (Jan. 2) 1937.

28. Blackfan, K. D., and Wolbach, S. B.: Vitamin A Deficiency in Infants: A Clinical and Pathological Study, J. Pediat. **3**:679-706 (Nov.) 1933.

and Hu [29] and by Loewenthal,[30] consists of a fairly characteristic keratotic papular lesion of varying size occurring especially on the thighs and extensor surfaces of the arms and legs. It is more common among adults than children and involves principally pilosebaceous follicles. A somewhat similar lesion, occurring in the presence of vitamin C deficiency, has been reported by Scheer and Keil.[31]

The presence of one or more of the foregoing signs might constitute good presumptive evidence of vitamin A deficiency, and this presumption would be greatly strengthened by the disappearance of the noted symptoms and signs following administration of pure vitamin A. However, the therapeutic test does not as yet constitute proof; for this, quantitative objective data will be required.

Because of the variability, and in some instances unreliability of methods of determining mild states of vitamin A deficiency, the frequency of such deficiency states is not clearly established. As a result of their studies, Jeans and Zentmire [32] offered evidence that in Iowa 26 per cent of a group of rural school children and 53 per cent of a group of village school children were deficient in vitamin A; in a group of urban children the proportion for the higher economic level was 56 per cent, for a middle level 63 per cent and for a low economic level 79 per cent. Park,[33] using the same method, tested 275 patients with a wide variety of diseases and found many with evidences of vitamin A deficiency. Frandsen [34] observed slight hemeralopia in 46 of 65 apparently healthy school children in Copenhagen.

VITAMIN B COMPLEX

There is ample chemical and physiologic evidence to indicate that the original water-soluble vitamin B is in reality a complex and consists of several distinct chemical entities. In the past years two factors, one a heat-labile vitamin, B_1, and the other a heat-stable vitamin, B_2, or G, were recognized. Other factors, including vitamins B_3, B_4 and B_5, have been described but not universally recognized. In a recent

29. Frazier, C. N., and Hu, C. K.: Cutaneous Lesions Associated with a Deficiency in Vitamin A in Man, Arch. Int. Med. **48**:507-514 (Sept.) 1931.

30. Loewenthal, L. J. A.: A New Cutaneous Manifestation in the Syndrome of Vitamin A Deficiency, Arch. Dermat. & Syph. **28**:700-708 (Nov.) 1933.

31. Scheer, M., and Keil, H.: Follicular Lesions in Vitamin A and C Deficiencies, Arch. Dermat. & Syph. **30**:177-185 (Aug.) 1934.

32. Jeans, P. C., and Zentmire, Zelma: The Prevalence of Vitamin A Deficiency Among Iowa Children, J. A. M. A. **106**:996-997 (March 21) 1936.

33. Park, I. O.: Preliminary Observations on Vitamin A Deficiency as Shown by Studies with the Visual Photometer, J. Oklahoma M. A. **28**:357-364 (Oct.) 1935.

34. Frandsen, H.: Investigation of Hemeralopia as Evidence of Minor Degrees of Vitamin A Deficiency, Nutrition Abst. & Rev. **4**:621-622, 1935.

summary of this problem, Peters [35] revealed that at least six entities compose the vitamin B complex, as follows:

Vitamin B_1 (aneurin or torulin)
Vitamin B_2 (G) { lactoflavine / vitamin B_6 (rat antidermatitis)
Vitamins B_3 and B_5 (including the chicken antipellagra factor)
Vitamin B_4 (position at present obscure)

The relation of these factors to the factors of the human antipellagra (P. P.) substance, to black tongue of dogs, to heart block of pigeons and possibly to other growth factors is not as yet clear, nor is it evident how many of these, other than vitamin B_1 and perhaps vitamin B_2, are essential for man. The delay in elucidating the nature of and the relation between the various factors is occasioned by the extreme difficulty of the experimental work and the variability in requirements of various test animals.

Vitamin B_1, which has been synthesized, is a pyrimidine thiazole (sulfur-nitrogen-carbon ring) compound, according to Williams.[36] Lactoflavine, which is one of the components of vitamin B_2 (G), also has been synthesized; it is allied to the purines, pyrimidines and nucleotides and has as its principal component the iso-alloxazine nucleus. The chemical composition and structure of the other components of the vitamin B complex are unknown.

Vitamin B_1.—It has been recognized for many years that vitamin B_1 is essential for growth, probably because of its influence in tissue oxidation, particularly in oxidation of carbohydrates. In 1929 Kinnersley and Peters [37] produced evidence that there was an increased amount of lactic acid in the brains of pigeons in terminal stages of vitamin B_1 deficiency as compared to that in the brains of normal pigeons. Subsequently Peters and Thompson [38] and Sherman and Elvehjem [39] revealed the importance of vitamin B_1 in the oxidation of pyruvic acid; in fact, the vitamin appears to be an essential catalyst in

35. Peters, R. A.: The Vitamin B Complex, Brit. M. J. **2**:903-905 (Nov. 7) 1936.

36. Williams, quoted by Peters.[35]

37. Kinnersley, H. W., and Peters, R. A.: Observations upon Carbohydrate Metabolism in Birds: I. The Relation Between the Lactic Acid Content of the Brain and the Symptoms of Opisthotonus in Rice-Fed Pigeons, Biochem. J. **23**: 1126-1136, 1929.

38. Peters, R. A., and Thompson, R. H. S.: Pyruvic Acid as an Intermediary Metabolite in the Brain Tissue of Avitaminous and Normal Pigeons, Biochem. J. **28**:916-925, 1934.

39. Sherman, W. C., and Elvehjem, C. A.: In Vitro Studies on Lactic Acid Metabolism in Tissues from Polyneuritic Chicks, Biochem. J. **30**:785-793 (May) 1936; In Vitro Action of Crystalline Vitamin B_1 on Pyruvic Acid Metabolism in Tissues from Polyneuritic Chicks, Am. J. Physiol. **117**:142-150 (Sept.) 1936.

the oxidation of pyruvic acid. As Peters and Thompson have pointed out, the extensive evidence for this fact can be summarized by saying that vitamin B_1 can be shown in vitro to have a specific catalytic effect on the brain tissue of pigeons suffering from deficiency of this vitamin and that pyruvic acid accumulates in the blood of animals, and probably of man, suffering from deficiency of vitamin B_1. The accumulation of lactic acid in the blood and tissues, which is a marked feature of vitamin B_1 deficiency and of beriberi in man, may be explained by the suggestion that the oxidation of lactic acid is inhibited at the stage of pyruvic acid. These changes in the nervous system probably explain many of the symptoms of vitamin B_1 deficiency; the remaining symptoms may be attributable to the influence of the vitamin on carbohydrate metabolism in tissues other than the brain. The effect of consumption of large quantities of carbohydrate on the requirement of vitamin B_1 has been of particular interest in this respect. Stepp and Schroeder [40] have reported the first case of relative beriberi in man, attributable to consumption of excessive carbohydrate (in their case from 500 to 1,500 Gm. of sugar daily).

Previous evidence suggesting a sparing action of a diet high in fat on the vitamin B_1 requirement has been denied by Sure and Buchanan [41] and by Westenbrink.[42] Of interest also is the work of Cowgill and Dann [43] on the failure of dinitrophenol to influence the vitamin B_1 requirement of dogs. It is generally accepted that elevation of the basal metabolic rate leads to an increased requirement for vitamin B_1. In these studies of Cowgill and Dann the average increase in the basal metabolic rate was 28 per cent, and yet there was no demonstrable effect on the vitamin B_1 requirement, probably because the important factor in determining the requirement of the vitamin is the total and not the basal metabolism.

The daily requirement for vitamin B_1 has been expressed by Cowgill [44] as about 300 U. S. P. units for a man weighing 70 Kg. Harris

40. Stepp, W., and Schroeder, H.: Beriberierkrankung beim Menschen hervorgerufen durch übermässigen Zuckergenuss, München. med. Wchnschr. **83**:763-764 (May 8) 1936.

41. Sure, B., and Buchanan, K. S.: Avitaminosis: Influence of High Fat-Containing Diets on Vitamin B_1 Requirements, Proc. Soc. Exper. Biol. & Med. **33**:75-76 (Oct.) 1935.

42. Westenbrink, H. G. K.: Physiologic Action of Vitamin B_1, Nutrition Abst. & Rev. **5**:944 (April) 1936.

43. Cowgill, G. R., and Dann, Margaret: The Failure of Dinitrophenol to Influence the Vitamin B Requirement, Yale J. Biol. & Med. **8**:501-509 (May) 1936.

44. Cowgill, G. R.: The Vitamin B Requirement of Man, New Haven, Conn., Yale University Press, 1934.

and Leong [45] calculated the requirement as 250 to 500 international units daily (about 1 mg. of crystalline vitamin). Baker and Wright [46] have reemphasized the fact that vitamin B_1 is not abundant in most foods. Most fresh foods contain about 1 international unit per gram, but the variability in this factor and the amount of the vitamin destroyed by processing of foods must be taken into consideration in any calculation of the content of the diet. It is exceedingly important to recall that during the process of digestion and alimentation there may be destruction or failure of absorption of vitamins and that even though the diet contains an adequate supply, a deficiency state may result. Scheunert and Schieblich [47] have shown, for example, that in dogs with an ileac fistula at least 66.6 per cent of vitamin B_1 administered by mouth (and a considerable amount of vitamin B_2) was absorbed in the stomach or small intestine.

A method of corroborating clinical impressions of mild states of vitamin B_1 deficiency may result from studies now in progress on urinary excretion of this vitamin. Helmer,[48] Harris and Leong and Roscoe [49] have published their results in the past year, and by biologic tests all have found appreciable quantities of the vitamin in urine. According to Harris and Leong, the daily output of vitamin B_1 in the urine of 9 healthy adults on "normal" diets amounted to from 12 to 35 international units, with an average of 20. This represented only 5 to 8 per cent of the intake. Variations could be noted when the vitamin B_1 content of the diet was increased or decreased, and the conclusion was reached that a daily excretion of less than 12 international units supports the presumption that the diet has less than a normal allowance of vitamin B_1. Roscoe said she was less convinced of the value of the estimation because of the variability in amounts excreted by normal subjects; in fact, in the urine of some, vitamin B_1 appeared not to be excreted in measurable quantities, although the intake was "normal." In addition, when vitamin B_1 was added to the diet in definite amounts, it was excreted by some and retained by other "normal" subjects. The vitamin B_1 content of the blood is at present being studied. These tests also depend on biologic methods, and in unpublished data Meiklejohn [50]

45. Harris, L. J., and Leong, P. C.: Vitamins in Human Nutrition: The Excretion of Vitamin B_1 in Human Urine and Its Dependence on the Dietary Intake, Lancet **1**:886-894 (April 18) 1936.

46. Baker, Audrey Z., and Wright, Margaret D.: The Vitamin B_1 Content of Foods, Biochem. J. **29**:1802-1807, 1935.

47. Scheunert, A., and Schieblich, M.: Ueber die Resorption von Vitamin B um Dummarm, Nutrition Abstr. & Rev. **5**:946 (April) 1936.

48. Helmer, O. M.: Vitamin B_1 and B_2 Content of Human Urine, Proc. Soc. Exper. Biol. & Med. **32**:1187-1188 (April) 1935.

49. Roscoe, Margaret H.: The B-Vitamins in Human Urine, Biochem. J. **30**:1053-1063 (June) 1936.

50. Meiklejohn, A. P., quoted by Peters.[35]

reported the normal value for man to be 4 international units (8.5 micrograms ± 1) for each hundred cubic centimeters of blood.

It has long been recognized that deficiency of vitamin B_1 leads to the development of beriberi. However, gradually accumulating evidence indicates that it may be a significant factor in leading to disturbances of the eye, of the nervous system, of the cardiovascular apparatus and of the gastro-intestinal tract and may cause diabetes and edema as well as other symptoms. Of chief clinical interest is the effect on the nervous and cardiovascular systems. Strauss [51] demonstrated clearly the etiologic relationship of vitamin B_1 to so-called alcoholic polyneuritis. Reports from other clinics have substantiated this and have recorded therapeutic value in the administration of large quantities of vitamin B_1 in the treatment of the condition. Jolliffe, Colbert and Joffe [52] have offered further evidence of this relationship by careful studies of the diets of 42 alcoholic addicts. They demonstrated that in their series the intake of vitamin B_1 of every alcoholic addict who had polyneuritis was estimated to be inadequate (Cowgill's formula); none of the addicts whose intake of vitamin B_1 was estimated as adequate had polyneuritis, and every addict whose intake of this vitamin was estimated as having been absolutely deficient for twenty-one days had polyneuritis. Subsequently, Jolliffe and Colbert [53] presented further evidence of the effects of vitamin B_1 in the treatment of "alcoholic" polyneuritis. In studies of a group of chronic alcoholic addicts with uncomplicated polyneuritis who were given diets containing slightly inadequate or barely adequate quantities of vitamin B_1, no improvement was noted in the objective signs of peripheral neuritis over a period of one month. The condition of subjects whose treatment consisted of an intake of vitamin B_1 that was approximately twice their predicted requirement improved but not as rapidly as, or in degree equal to, that of subjects who received four times their requirement of vitamin B_1. It is possible that fractions of the vitamin B complex other than vitamin B_1 were therapeutically significant in these cases, since a preparation of autolyzed brewer's yeast was used. It is particularly interesting in this respect to record the failure of Wechsler, Jervis and Potts [54] to produce the clinical or pathologic syndrome of polyneuritis in monkeys. Deficient intake, relative and absolute, of vitamin B_1 alone or combined

51. Strauss, M. B.: The Etiology of "Alcoholic" Polyneuritis, Am. J. M. Sc. **189**:378-382 (March) 1935.

52. Jolliffe, N.; Colbert, C. N., and Joffe, P. M.: Observations on the Etiologic Relationship of Vitamin B (B_1) to Polyneuritis in the Alcohol Addict, Am. J. M. Sc. **191**:515-526 (April) 1936.

53. Jolliffe, N., and Colbert, C. N.: The Etiology of Polyneuritis in the Alcohol Addict, J. A. M. A. **107**:642-647 (Aug. 29) 1936.

54. Wechsler, I. S.; Jervis, G. A., and Potts, H. D.: Experimental Study of Alcoholism and Vitamin B Deficiency in Monkeys, Bull. Neurol. Inst. New York **5**:453-475 (Aug.) 1936.

with acute and chronic alcoholism, did not produce clinical or pathologic features suggesting polyneuritis. Whether this unusual resistance to alcoholic intoxication and vitamin B_1 deficiency represents a species difference is unknown.

Cardiovascular disturbances involving particularly the heart and the capillaries are known to be associated with beriberi and have led to the designation "beriberi heart." This condition, which has been thoroughly described clinically and pathologically by Wenckebach,[55] is rarely observed in the United States. Recent studies made by Weiss and Wilkins [56] are of particular interest because an attempt has been made to describe the cardiovascular symptoms and signs of a group of patients who gave evidence of mild and moderate deficiency of vitamin B_1 and to delineate the cardiovascular conditions in which vitamin B_1 may be of therapeutic value. From a group of patients in the Boston City Hospital 97 were selected in whom disturbances of cardiovascular function seemed related to nutritional factors. Patients were selected in whom a cardiovascular disturbance was present and was unexplained on the basis of any factors ordinarily recognized as being of etiologic significance in circulatory failure. In all instances the history gave evidence of an unbalanced diet, and many patients showed other signs of deficiency states, such as "alcoholic" polyneuritis. As evidence of a direct relationship between cardiovascular symptoms and deficiency of vitamin B components, Weiss and Wilkins have used the following criteria: the history of an unbalanced diet; the beneficial response to foods rich in vitamin B or to concentrates or crystals of vitamin B_1; the simultaneous presence of other clinical manifestations recognized as deficiency states, such as polyneuritis; the absence of other recognizable etiologic factors of cardiac disease; the electrocardiographic changes which disappear after administration of vitamin B_1, and the similarity of the clinical syndrome and histologic picture of the heart muscle to those observed in beriberi in other parts of the world. It is clearly recognized that the evidence is presumptive and that proof has not been established. In studies of these patients the principal conclusions reached included the observations that dysfunction of the cardiovascular system might develop as a result of an unbalanced diet (especially one lacking in vitamin B) and that such dysfunction could affect both a previously normal and a previously damaged cardiovascular apparatus. The authors stated that they felt that these abnormalities depended partly on changes in the nervous system and partly on changes in the myocardium. The principal symptoms were simple tachycardia; vagus

55. Wenckebach, K. F.: Das Beriberi-Herz: Morphologie, Klinik, Pathogenese, Pathologie und Klinik in Einzeldarst, Berlin, Julius Springer, 1934, vol. 6.

56. Weiss, S., and Wilkins, R. W.: The Value of Cardiovascular Disturbances in Vitamin Deficiency States, Tr. A. Am. Physicians **51**:341, 1936.

reflex irritability, with bradycardia or with asystole and syncope, and failure of the right or left side of the heart, peripheral arteriolar dilatation and vasomotor collapse, with vascular constriction, in various combinations. In one group of patients these changes disappeared rapidly, and in another they disappeared slowly after rest and an adequate dietary intake. Electrocardiographic changes were noted in all but 3 of 38 patients and consisted principally of changes in the T waves, in low amplitude and in prolongation of the electrical systole (Q-T), which usually disappeared under therapeutic measures. Histologic changes observed in the cardiac muscle in several patients were observed to be similar to those described by Wenckebach, but they were not considered characteristic or specific of deficiency states. Weiss and Wilkins expressed the opinion that the conditions they described were actually more frequent than has been noted previously. They wrote that such conditions should be looked for principally in examination of alcoholic addicts and less frequently in examination of pregnant women, of persons without work, of those living in conditions of poverty, of food cranks, of diabetic patients and of those with certain types of gastrointestinal disease. These groups of persons rarely perform hard work and this may be one of the factors which accounts for the great variability which has been noted in the degree of deficiency and in the variability or absence of symptomatic response.

It is extremely important not to ascribe to vitamin B deficiency cardiovascular symptoms or signs which cannot readily be explained on the basis of ordinary and well recognized conditions. Much more evidence will have to be presented before the field of cardiovascular changes in relation to vitamin B deficiency can be closely delineated. It is equally important to emphasize that the promiscuous use of preparations of vitamin B for relief of symptoms in all types of cardiovascular disease is useless and might prove dangerous. Weiss [57] pointed out that his studies of the effect of vitamin B_1 on the heart and circulation of normal subjects, in the presence of various types of organic heart disease and in the presence of different types of edema, revealed no changes in heart rate, in electrocardiographic tracings, in hemodynamics or in edema, even though a dose as large as 30 or 40 mg. of crystalline vitamin B_1 was given in a single injection.

Rabinowitz and Rogers [58] have reported an interesting case of a child 4 years of age who had a large heart, a rapid and irregular pulse, gallop rhythm, a precordial thrill and loud systolic and diastolic murmurs, with evidence also of scurvy and rickets. Four months after

57. Weiss, Soma: Personal communication to the author.

58. Rabinowitz, L., and Rogers, E. J.: Reversion of Cardiac Enlargement in a Four Year Old Child Following Treatment for Avitaminosis, New England J. Med. **215**:621-623 (Oct. 1) 1936.

dietary treatment the foregoing signs and symptoms had cleared, and the size of the heart was normal.

The mechanism of formation of edema in relation to vitamin B_1 deficiency is still not clear. In some instances the edema is probably dependent, in part at least, on circulatory failure and in others on associated decrease in the plasma proteins; while in some cases, such as that of Elsom,[59] it remains unexplained. A relationship which might exist between vitamin B_1 and carbohydrate metabolism in diabetes and the possible therapeutic value of crystalline vitamin B_1 in the treatment of diabetes was mentioned in last year's review.[60] Acute and chronic disorders of the optic nerve and perhaps of the ocular muscles, hemorrhagic lesions of the retina and optic neuritis all have been ascribed to deficiency of vitamin B_1.

The occurrence of anorexia, achlorhydria, atrophy of the lingual papillae and hypotonicity and hypomotility of the gastro-intestinal tract all have been noted as evidence of vitamin B_1 deficiency. In an interesting study of the possible effect of vitamin B_1 deficiency on the gastric juice of man, Alvarez and his associates[61] made daily observations on the gastric juice of 2 subjects over a period of six weeks while on a diet sufficiently deficient in vitamin B_1 to make the vitamin-calory ratio 1.2 (normal minimum, 1.8—Cowgill). No signs of vitamin B_1 deficiency developed, although the value for hemoglobin distinctly dropped, and changes were not noted in the concentration of hydrochloric acid or pepsin in the gastric juice. In studies of experimental animals Simpson[62] could not find atrophy, ulceration or erosion of the gastric mucosa of albino rats which were on a diet deficient in vitamin B_1, and he said he did not believe the slight changes he noted could be of any importance in the genesis of ulcer. These changes were moderate congestion and cellular infiltration. Kik, Sure and Buchanan[63] did not observe in the rat noteworthy changes in digestive efficiency of either the proteolytic or the amylolytic enzyme in the presence of deficiency of vitamin B or G. There was, however, a marked decrease in the

59. Elsom, K. O.: Experimental Study of Clinical Vitamin B Deficiency, J. Clin. Investigation **14**:40-51 (Jan.) 1935.

60. Wilder, R. M., and Wilbur, D. L.: Diseases of Metabolism and Nutrition: Review of Certain Recent Contributions, Arch. Int. Med. **57**:422-471 (Feb.) 1936.

61. Alvarez, W. C.; Pilcher, F.; Foley, Mary A.; Mayer, Annette, and Osterberg, A. E.: The Effects on the Gastric Juice of Man of Six Weeks' Deprivation of Vitamin B_1, Am. J. Digest. Dis. & Nutrition **3**:102-107 (April) 1936.

62. Simpson, C. K.: Observations upon Gastritis, Guy's Hosp. Rep. **86**:120-128 (Jan.-April) 1936.

63. Kik, M. C.; Sure, B., and Buchanan, Kathryn S.: Enzymic Efficiency in Avitaminosis: III. Influence of Vitamin B_1 and G Deficiencies on the Concentration of Blood and Tissue Enzymes, Am. J. Digest. Dis. & Nutrition **3**:490-492 (Sept.) 1936.

digestive efficiency of pancreatic esterase, and there was a marked decrease in the concentration of pancreatic and hepatic lipase in the presence of vitamin B deficiency, which suggests a disturbance in digestion of fats in this type of avitaminosis.

Vitamin B_3.—The importance of this factor in nutrition of man has not been established.

Vitamin B_4.—Little is known of the physiology of vitamin B_4. It may be related to certain adenine nucleotides or nucleosides. Elvehjem [64] has expressed the belief that this factor probably will find an important place in nutrition of man and in the treatment of certain disorders of the brain. It is not abundant in foods and is easily destroyed. Some workers believe that deficiency of vitamin B_4 is relieved by large doses of vitamin B_1 and therefore doubt the existence of vitamin B_4.

Vitamin B_5.—The status of this factor is questionable.

Vitamin B_6.—This factor, which is one of the principal components of vitamin B_2, or G, is identical with the "factor Y" of Chick, Copping and Edgar [65] and with György's [66] vitamin B_6. Its absence leads to the development of "rat pellagra." The factors of "rat pellagra," "chick pellagra" and "human pellagra" are apparently not identical, and consequently the relation of vitamin B_6 to pellagra of man remains to be defined.

Pellagra.—The etiology of pellagra is still not entirely clear. Deficiency of vitamin B_2, or G, long has been associated with this disease, but a clearcut etiologic relationship has not been established. Vitamin B_2 (G) has been found to consist of at least two factors, one of which, lactoflavin, has been shown by Dann [67] to be of no therapeutic value in pellagra of man. The relation of the other factor, B_6, the chemical nature of which is uncertain, is not clear either. Elvehjem, for instance, stated that black tongue of dogs, which generally is accepted as identical with pellagra of man, is completely relieved by administration of a filtrate which remains after removal of flavins from vitamin B_2 (G). On the other hand, in their observations Birch, György and Harris [68]

64. Elvehjem, C. A.: Present Status of the Vitamin B Complex, Am. J. Pub. Health **25**:1334-1339 (Dec.) 1935.

65. Chick, Harriette; Copping, Alice M., and Edgar, Constance E.: The Water-Soluble B-Vitamins: IV. The Components of Vitamin B_2, Biochem. J. **29**:722-734, 1935.

66. György, P.: Investigations on Vitamin B_2 Complex: The Distribution of Lactoflavin and of "Pellagra-Preventing Factor" (Vitamin B_6) in Natural Products of Animal Origin, Biochem. J. **29**:760-766, 1935.

67. Dann, W. J.: The Vitamin G Complex in Rat Dermatitis and Human Pellagra, J. Biol. Chem. **114**:xxiv-xxv, 1936.

68. Birch, T. W.; György, P., and Harris, L. J.: I-VI. The Vitamin B_2 Complex: Differentiation of the Antiblack-Tongue and the "P.-P." Factors from Lactoflavin and Vitamin B_6 (So-Called "Rat Pellagra" Factor), Biochem. J. **29**:2830-2850, 1935.

and Dann [69] have been unable to relate vitamin B_6 to black tongue of dogs or to pellagra of man. Birch and his associates have reported the occurrence of pellagra of man when the diet was high in vitamin B_6.

Although, as has been noted, there is disagreement as to the nature of the significant dietary factors in pellagra, Sydenstriker and his collaborators [70] suggested the existence of an "intrinsic" factor, which is deficient in pellagra. These workers offered the hypothesis that the intrinsic factor is present in gastric juice and that it makes possible utilization of minimal quantities of extrinsic factors. Variability in the capacity to retain or regenerate the intrinsic factor may explain some of the variabilities in therapeutic response of pellagrous patients.

The characteristic early cutaneous lesions of pellagra occur principally on exposed surfaces, and it has long been accepted that exposure to sunlight is a precipitating factor in this typical distribution. Spies [71] recently has studied this phase of the disease and has reported that pellagrous lesions occur in the absence of sunlight and may heal in the presence of exposure to sunlight or to ultraviolet radiation. Spies emphasized that pellagra should be considered a systemic disease and not a cutaneous condition and that under certain circumstances, still matters of conjecture, sunlight may act as an irritant and precipitate the cutaneous lesions of the disease.

Cardiac symptoms are rarely reported in pellagra, but Feil [72] reported abnormal electrocardiographic tracings for half of 38 patients with moderate to severe pellagra. In 14 of the 19 patients in whom changes were detected no other abnormalities which could influence the tracing were observed. The changes noted were inversion of the T wave in leads I or II or both, a Pardee type of S-T wave and a large T wave. Feil expressed the opinion that the heart is physiologically disturbed in this disease.

Of much practical clinical value is the report of Blankenhorn and Spies [73] on the significance, recognition and treatment of oral complications of chronic alcoholism and of alcoholic pellagra. Approximately

69. Dann, W. J.: The Vitamin G Complex: Non-Identity of Rat Dermatitis Due to Vitamin B_6 Deficiency and Dermatitis of Human Pellagra, J. Nutrition **11**:451-462 (May) 1936.

70. Sydenstriker, V. P.; Armstrong, E. S.; Derrick, C. J., and Kemp, P. S.: On the Existence of Intrinsic Deficiency in Pellagra: Preliminary Report, Am. J. M. Sc. **192**:1-9 (July) 1936.

71. Spies, T. D.: Relationship of Pellagrous Dermatitis to Sunlight, Arch. Int. Med. **56**:920-926 (Nov.) 1935.

72. Feil, H.: Clinical Study of Electrocardiogram and of Phases of Cardiac Systole in Pellagra, Am. Heart J. **11**:173-184 (Feb.) 1936.

73. Blankenhorn, M. A., and Spies, T. D.: Oral Complications of Chronic Alcoholism: Significance, Recognition and Treatment, J. A. M. A. **107**:641-642 (Aug. 29) 1936.

60 per cent of 200 alcoholic addicts were found to have on the mouth and tongue specific lesions of widespread stomatitis. The tongue becomes swollen so that impression of the teeth can be seen on its surface; it becomes bright red and ulceration may occur. The gums and mucous membrane may share in this process. Early treatment, consisting of a nutritious diet of 4,000 calories and 75 Gm. of yeast or of liver extract daily, caused the lesions to disappear.

Methods of Recognition and the Frequency of States of Deficiency from Lack of the Components of the Vitamin B_1 Complex.—Knowledge of these matters remains in the process of evolution. According to Youmans, no reliable symptoms, signs or diagnostic tests are available for detection of conditions of minimal vitamin B_1 deficiency. However, a variety of clinical symptoms exist which should lead one to suspect the possibility of such deficiency. The occurrence of neuritis of the peripheral or optic nerves, of circulatory changes previously noted, of unexplained edema and of vague but suggestive digestive symptoms, such as anorexia, achlorhydria and poor intestinal tonicity, particularly if patients have been on an inadequate diet, should lead perhaps to a suspicion of deficiency. Estimation, with Cowgill's formula, of the vitamin B_1 requirement of the subject and of his previous intake might be helpful as additional evidence. As yet estimations of the vitamin B_1 content of the blood and urine require extensive laboratory and biologic facilities and are therefore not practicable for ordinary use; also the lower limit of vitamin adequacy has not been clearly established for man. Therapeutic tests with crystalline vitamin B_1 also are of diagnostic value, but favorable response to injections of this substance is not proof that the patient suffered from a deficiency of the vitamin.

The diagnosis of pellagra still depends on clinical judgment. Glossitis, diarrhea, digestive disturbances and nervous and mental disorders are no more than suggestive. The cutaneous symptoms may be characteristic. Response of such symptoms to administration of yeast and other preparations rich in the vitamin B complex may constitute further evidence.

The frequency of lesions resulting from vitamin B deficiency is uncertain. The observations of Weiss and Wilkins, of Youmans and of Scott and Herrmann [74] suggest that states of vitamin B_1 deficiency may be more common than has previously been thought, but more objective evidence is necessary before certain knowledge of the frequency of the disorder can be obtained. Attention should be directed to the occurrence of so-called secondary pellagra in the northern part of the United States, namely, pellagra secondary to or associated with organic disease of the digestive tract, particularly obstructing and malignant diseases.

74. Scott, L. C., and Herrmann, G. R.: Beriberi ("Maladie des Jambes") in Louisiana, with Especial Reference to Cardiac Manifestations, J. A. M. A. **90**:2083-2090 (June 30) 1928.

VITAMIN C

In an excellent review of the chemistry and physiologic activity of vitamin C, King [75] pointed out that the period since 1932 has witnessed the identification and establishment of the molecular structure of vitamin C, as well as many exact measurements of its physiochemical properties, its synthesis, its commercial production and the development of many methods of analysis and of detailed knowledge of its occurrence in plant and animal tissues. Moreover, a certain degree of correlation with specific enzyme systems has been worked out and steady but slow advance has been made in understanding its significance in relation to the health of man. As far as animal tissues are concerned, the two specific rôles for vitamin C which seem to have been clearly established are in respiratory function and in regulation of the colloidal condition of the intercellular substance. Its rôle in relation to respiratory function has to do with the vitamin serving as an agent for transporting hydrogen between unidentified metabolites and other carriers or molecular oxygen, by way of two or more oxidase enzyme systems. It appears likely that the vitamin affects directly or indirectly many additional types of chemical change. Clinical interest has been centered principally around the rôle of vitamin C in the regulation of the colloidal condition of the intercellular substance, because the hemorrhagic tendency which is so characteristic of scorbutic states is the result principally of alterations in the intercellular substance of capillary walls.

Vitamin C is water soluble and readily diffusible and therefore is usually easily absorbed from the gastro-intestinal tract. According to Klodt,[76] this absorption occurs principally in the upper part of the intestine. He expressed the belief that bile may aid in the absorption, since it retards oxidation of vitamin C in dilute solutions. Under normal circumstances variable amounts of the vitamin are lost in the stool or destroyed in the gastro-intestinal tract. Measurements of the vitamin C content of a large variety of tissues, as well as that of the blood and urine, have been made; in fact, the vitamin C content of a single cell can be estimated with a fair degree of accuracy. The vitamin C content is highest in glandular tissues and lowest in muscle and stored fat. Glick and Biskind,[77] using a microchemical method sensitive to ± 0.0001 mg. of vitamin C, have examined the content of this vitamin in the various tissues of cattle. The highest recorded value is in the pars intermedia of the pituitary body, which contains one and one-half

75. King, C. G.: Vitamin C, Ascorbic Acid, Physiol. Rev. **16**:238-262 (April) 1936.

76. Klodt, W.: Influence of Bile on Resorption of Vitamin C, abstr., J. A. M. A. **106**:2036 (June 6) 1936.

77. Glick, D., and Biskind, G. R., cited in Distribution of Cevitamic Acid in Tissues, editorial, J. A. M. A. **107**:1135-1136 (Oct. 3) 1936.

times more than the pars distalis of the pituitary body or the adrenal cortex. The amount present in the corpus luteum roughtly parallels the amount of luteal hormone, progesterone, in the ovary.

Methods of testing the vitamin C content of urine depend on the capacity of the vitamin as a reducing substance. The principle involved rests on the reduction of the vitamin in the urine by titration with the dye 2:6 dichlorophenol-indophenol. The principal sources of error include the presence of other reducing substances in urine and the destruction of vitamin C in urine which is allowed to stand without adequate preservative measures. Sendroy and Schultz [78] have shown that the important factors in the preservation of cevitamic acid in the urine are oxygen tension, temperature and p_H, particularly the first. Urine to be tested should be titrated immediately after it has been voided, or it may be preserved by addition of 10 per cent by volume of glacial acetic acid or it may be kept in a refrigerator in a small container from which air is excluded. Sendroy and Schultz estimated that their titrations approximated within 10 to 15 per cent of the total cevitamic acid content of the urine. A ferricyanide method of titration of urine for vitamin C has been used by Tauber and Kleiner.[79]

The quantity of vitamin C in the twenty-four hour output of urine of normal subjects is variable and depends principally on two factors: the first is the relative approach to saturation of the tissues of the subject, and the second is the intake of vitamin C during the period over which tests are made. Harris and Ray [80] placed the average in the twenty-four hour output of urine of normal subjects at from 30 to 33 mg. Johnson and Zilva [81] stated as their conclusion that there is no definite standard of normality as regards urinary excretion, while Wright [82] has found the average normal excretion to be from 20 to 30 mg. daily. However, Youmans and his colleagues [83] reported that

78. Sendroy, J., Jr., and Schultz, M. P.: Studies of Ascorbic Acid and Rheumatic Fever: Quantitative Index of Ascorbic Acid Utilization in Human Beings and Its Application to Study of Rheumatic Fever, J. Clin. Investigation **15**:369-383 (July) 1936.

79. Tauber, H., and Kleiner, I. S.: A Method for the Quantitative Determination of Ascorbic Acid (Vitamin C): The Vitamin C Content of Various Plant and Animal Tissues, J. Biol. Chem. **108**:563-570, 1935.

80. Harris, L. J., and Ray, S. N.: Diagnosis of Vitamin-C Subnutrition by Urine Analysis, with Notes on Antiscorbutic Value of Human Milk, Lancet **1**:71-77 (Jan. 12) 1935.

81. Johnson, S. W., and Zilva, S. S.: The Urinary Excretion of Ascorbic and Dehydro-Ascorbic Acids in Man, Biochem. J. **28**:1393-1408, 1934.

82. Wright, I. S.: The Present Status of the Clinical Use of Cevitamic Acid (Ascorbic Acid) (Crystalline Vitamin C), Am. J. M. Sc. **192**:719-735 (Nov.) 1936.

83. Youmans, J. B.; Corlette, M. B.; Akeroyd, J. H., and Frank, H.: Studies of Vitamin C Excretion and Saturation, Am. J. M. Sc. **191**:319-333 (March) 1936.

half of 16 normal controls whose diets were supposedly adequate excreted less than 20 mg. daily. These results suggest the variability which probably exists in normal subjects and emphasizes the fact that few, if any, conclusions can be drawn from isolated determinations of the urinary output of vitamin C.

Methods of determination of the reduced cevitamic acid content of the blood serum and plasma have been developed by Abt, Farmer and Epstein [84] and by Taylor, Chase and Faulkner.[85]

Taylor and his associates reported that in studies of 33 subjects who were free from infection or scurvy the average level of reduced cevitamic acid in the blood plasma was found to be 1.61 mg. per hundred cubic centimeters, with extreme values of 0.83 and 2.43 mg. Abt and his associates stated as their conclusion that values of less than 0.75 or 0.8 mg. of reduced cevitamic acid per hundred cubic centimeters of blood plasma indicate a subnormal intake of vitamin C. Wright, using the method of Abt, Farmer and Epstein, found the normal level in adults to rest between 0.7 and 1.3 mg. per hundred cubic centimeters of blood.

The classic clinical picture of scurvy is infrequently seen, but reports of subclinical and preclinical scurvy, diagnosis of which has been based principally on studies of capillary fragility or on the results of urinary excretion of a variety of test doses of vitamin C, have appeared frequently in the literature. It seems obvious that there is a wide zone of vitamin deficiency between scurvy and optimal health. How satisfactorily quantitative tests of the intake and output of vitamin C and of its concentration in the blood plasma of patients can be used to determine the position of a patient in this zone is uncertain. However, it must be emphasized that until more is known about the actual daily requirement of vitamin C, about the significance of saturation and about the clinical value of test doses, caution must be used in the interpretation of many conditions now called "subclinical" scurvy.

Studies of "capillary fragility," or "capillary resistance," have been used for several years as a measure of the adequacy or inadequacy of vitamin C nutrition. A variety of different methods of performing the test have been developed, and this has further tended to confuse the issue. Wright has well summarized the situation in pointing to the three distinct schools of thought in regard to the diagnostic significance of the method: 1. Those of one school believe that the phenomenon is useful and important and that a positive pressure method is probably

84. Abt, A. F.; Farmer, C. J., and Epstein, I. M.: Normal Cevitamic (Ascorbic) Acid Determinations in Blood Plasma and Their Relationship to Capillary Resistance, J. Pediat. **8**:1-19 (Jan.) 1936.

85. Taylor, F. H. L.; Chase, D., and Faulkner, J. M.: The Estimation of Reduced Ascorbic Acid in Blood Serum and Plasma, Biochem. J. **30**:1119-1125 (July) 1936.

the most satisfactory one. 2. Those of another school believe that the phenomenon is useful and important, but they feel that a negative pressure method is more reliable and acceptable. 3. Those of still another school feel that studies of the vitamin content of the urine and blood reveal the entire picture and that the capillary fragility tests are misleading and of little value.

Any one who takes the time to review the literature in regard to this interesting and important phase of nutrition cannot fail to be impressed by the variability of the results which have been reported. There can be no question that increased capillary fragility is nonspecific and occurs in a variety of conditions other than deficiency of vitamin C, such as thrombocytopenic purpura and increased capillary fragility resulting from the toxic effects of neoarsphenamine, carbon monoxide, scarlet fever and diphtheria, as well as anemia. Failure of patients with scurvy to give evidence of increased capillary fragility has been noted by Weld.[86] On the other hand, there is not always a clear-cut correlation between the levels of cevitamic acid in the plasma and the urine and the results of capillary fragility tests (Abt, Farmer and Epstein and Wright). It seems obvious, therefore, that final conclusions cannot be made as yet delineating the diagnostic value of the various methods. It is logical that a positive result of the capillary fragility test should lead to the suspicion of a state of deficiency of vitamin C and that much weight would be added to this suspicion if the test became negative after administration of cevitamic acid. However, if scurvy and prescorbutic states are attributable solely to deficiency of vitamin C, then final proof of the presence of such a condition will have to depend on the demonstration, by objective quantitative data, of a deficiency in levels in the plasma and urine or in the response to a test dose of vitamin C. As yet these values have not been satisfactorily defined for normal subjects.

The administration of test doses of vitamin C to determine the "saturation," "retention," "reserve" and "resaturation" of vitamin C has been reported to be of value in determining the nutritive status of a subject with respect to vitamin C or as a diagnostic test of a prescorbutic state. Some of these tests should prove to be of great value when normal standards have been established. It does not seem reasonable to suggest that a subject must be saturated with vitamin C in order to avoid being classed as one suspected of having prescorbutic or preclinical scurvy. There is considerable difference of opinion in regard to the value of such test doses. Youmans and his colleagues reported that, in general, tests of saturation correspond to the tests of daily excretion and the probable dietary intake of the vitamin and

86. Weld, C. B.: Capillary Resistance Test and Its Relation to Vitamin C and D, J. Pediat. **9**:226-233 (Aug.) 1936.

that a daily excretion of 20 mg. and an excretion of 30 per cent of a test dose (about 600 mg. in adults) are suggested as the lower limits of normal daily excretion and of saturation, respectively. Sendroy and Schultz, on the other hand, suggested that the urinary excretion test of cevitamic acid is largely affected by the two variable factors: relative approach to saturation of the tissues at the beginning of the test and the intake in the diet of the subject during the course of the test. If one can maintain this second factor constant by bringing about ingestion and absorption of fixed high doses of cevitamic acid, the results of the test may be taken as a measure of the first factor, namely, the approach to saturation. The investigators named therefore proposed that the total of seven days' excretion under conditions of high daily test dose of 250 mg. of cevitamic acid would be informative. Under such circumstances these workers have prepared a table of the "utilization coefficient" of vitamin C at various ages. In studies of the saturation and reserve of vitamin C, O'Hara and Hauck [87] reported that the amount of vitamin C necessary to restore the tissues to saturation after a month on a diet low in vitamin C ranged from 2,200 to 2,800 mg. when administered in daily doses of 200 mg. They estimated the tissue reserves at saturation to be about 2,500 to 3,000 mg. In their observations of the excretion of cevitamic acid Archer and Graham [88] found evidence that the percentage output is much more valuable evidence that a patient has scurvy than is the amount of cevitamic acid taken before the excretion increased or the amount excreted after a test dose. They suggested that one should measure the amount of cevitamic acid which must be given before the percentage output rises above 75 per cent.

The development of deficiency states does not always indicate a previously inadequate diet. Abnormalities of absorption and abnormal metabolic demands may precipitate such conditions in the face of an adequate diet. As Gagyi [89] has pointed out, there are two types of avitaminosis C. One is an alimentary type, and the other is a toxic type, usually observed in the course of infectious diseases. An excellent example of the alimentary type of scurvy is the case reported by Moncrieff [90] in which scurvy developed in an infant while it was on an adequate diet; the scurvy was promptly relieved by intravenous

87. O'Hara, Patricia H., and Hauck, Hazel M.: Storage of Vitamin C by Normal Adults Following a Period of Low Intake, J. Nutrition **12**:427-413 (Oct. 10) 1936.

88. Archer, H. E., and Graham, G.: Some Observations on the Excretion of Ascorbic Acid, Lancet **1**:710-713 (March 28) 1936.

89. Gagyi, J.: Ueber die bactericide und antitoxische Wirkung des Vitamin C, Klin. Wchnschr. **15**:190-195 (Feb. 8) 1936.

90. Moncrieff, A., quoted in Unexpected Rickets and Scurvy, annotation, Lancet **1**:36 (Jan. 4) 1936.

administration of vitamin C. The inhibitory effect which the vitamin has on diphtheria toxin, and probably also on other products of pathogenic organisms, may be one of the normal defense mechanisms of man. It probably explains, in part at least, the frequently observed low values for cevitamic acid in the blood and urine in the presence of infections. The prophylactic and therapeutic use of vitamin C in infections has not produced clearcut results. Encouraging reports have been made of its use in association with hormones of the adrenal cortex in the presence of diphtheria, although it does not supplant diphtheria antitoxin. Encouraging studies of Jungeblut [91] have suggested that it may be of value in inactivation of poliomyelitis virus in the experimental animal. Wright has reported that as a prophylactic against acute infections, such as tonsillitis, otitis media and abscess, large doses of vitamin C were not of value. Heise and Martin [92] expressed the belief that in pulmonary tuberculosis there is a rough parallelism between the activity of the disease and the daily excretion of vitamin C in the urine when the patient is on a controlled diet. They estimated that the patient who has tuberculosis requires from 55 to 138 mg. of cevitamic acid to maintain a normal rate of excretion, as compared with the normal requirement of from 15 to 30 mg. Hasselbach [93] placed the daily requirement, in the presence of active pulmonary tuberculosis, at the equivalent of from 100 to 150 mg. of orange juice.

The relation of gastro-intestinal abnormalities to absorption of vitamin C is indicated by the studies of Einhauser,[94] who reported that when patients have what he called "gastro-intestinal catarrh," there is disturbance in absorption of vitamin C. This is particularly true if patients have achlorhydria; then more rapid oxidative decomposition of vitamin C is said to result from the increased alkalinity of the intestinal content, as well as from the pathologic bacterial flora, which destroys vitamin C. Whether vitamin C is a significant factor in the etiology of gastric and duodenal ulcer, or perhaps in hemorrhages which occur from such lesions, is an important practical point. Schultzer's [95] studies indicated that the capillary resistance in such cases is not abnor-

91. Jungeblut, C. W.: Inactivation of Poliomyelitis Virus in Vitro by Crystalline Vitamin C (Ascorbic Acid), J. Exper. Med. **62**:517-521 (Oct.) 1935.

92. Heise, F. H., and Martin, G. J.: Ascorbic Acid Metabolism in Tuberculosis, Proc. Soc. Exper. Biol. & Med. **34**:642-644 (June) 1936.

93. Hasselbach, F.: Vitamin C und Lungentuberkulose, Ztschr. f. Tuberk. **75**:336-347 (July) 1936.

94. Einhauser, M.: C-Vitamin und Gastroenteritis, Ztschr. f. d. ges. exper. Med. **98**:461-477, 1936; abstr., J. A. M. A. **107**:548 (Aug. 15) 1936.

95. Schultzer, Paul: Studies on Capillary Resistance: III. Improbability of C Avitaminosis as Etiological Factor in Peptic Ulcer, Acta med. Scandinav. **83**:555-564, 1934.

mal as compared with the normal. However, Archer and Graham [96] reported that in 9 patients with ulcer they found less saturation with vitamin C than in 2 control subjects who gave rather low values for the vitamin. Similarly, Harris, Abbasy, Yudkin and Kelly [97] found in patients with ulcer in a large hospital an average urinary excretion of 5.6 mg. of vitamin C in twenty-four hours, while the average for 74 adult patients in the hospital was 8.9 mg. It seems clear that in most of these cases the low values were related to a low intake of vitamin C on ordinary therapeutic diets for ulcer. It is questionable if lack of vitamin C is more than a secondary factor in causation of ulcer under such circumstances. Its relation to hemorrhage from ulcer is still unsettled and obviously requires close scrutiny.

Interesting but conflicting reports of the relation of vitamin C to pigmentation of the skin have appeared recently. Szent-Györgyi,[98] in 1934, reported decrease in the pigmentation in Addison's disease following the use of cevitamic acid. Wilkinson and Ashford [99] studied 3 patients with Addison's disease and found in all of them deficiency in vitamin C; they did not obtain distinct change in pigmentation at first but definitely less pigmentation after vitamin C had been administered for some time. In a case of pernicious anemia, with pigmentation of the face, Schroeder and Einhauser [100] did not observe change in the pigmentation following the use of liver extract but prompt lessening of the pigmentation when 300 mg. of synthetic vitamin C was given intravenously for fourteen days.

Further attempts to relate rheumatic fever and chronic infectious arthritis to deficiency of vitamin C have been made by Rinehart,[101] on the basis of the similarity of lesions observed in man in these conditions and those observed in scorbutic animals with added infection. The studies of Sendroy and Schultz and of Schultz [102] failed to support the concept that a condition of deficiency of cevitamic acid is a predis-

96. Archer, H. E., and Graham, G.: The Subscurvy State in Relation to Gastric and Duodenal Ulcer, Lancet **2**:364-366 (Aug. 15) 1936.

97. Harris, L. J.; Abbasy, M. A.; Yudkin, J., and Kelly, S.: Vitamins in Human Nutrition: Vitamin-C Reserves of Subjects of the Voluntary Hospital Class, Lancet **1**:1488-1490 (June 27) 1936.

98. Szent-Györgyi, A., quoted by Wright and Lilienfeld.[103]

99. Wilkinson, J., and Ashford, C. A.: Vitamin C Deficiency in Addison's Disease, Lancet **2**:967 (Oct. 24) 1936.

100. Schroeder, H., and Einhauser, M.: Ueber einen Zusammenhang zwischen gestörter Vitamin-C-Resorption und pathologischer Pigmentierung bei Gastroenteritis und Achylia gastrica, München. med. Wchnschr. **83**:923-925 (June 5) 1936.

101. Rinehart, J. F.: An Outline of Studies Relating to Vitamin C Deficiency in Rheumatic Fever, J. Lab. & Clin. Med. **21**:597-604 (March) 1936.

102. Schultz, M. P.: Studies of Ascorbic Acid and Rheumatic Fever: Test of Prophylactic and Therapeutic Action of Ascorbic Acid, J. Clin. Investigation **15**:385-391 (July) 1936.

posing factor in the causation of rheumatic fever; these studies revealed also that clinical manifestations of this disease were not demonstrably affected by the oral or intravenous administration of vitamin C over periods of several months. Certainly further observations should be carried out in this interesting field.

In view of the hemorrhagic tendency in scurvy, it was obvious that attempts would be made to relate all types of hemorrhagic diseases to vitamin C deficiency and to treat them with the vitamin. Disappointment has followed almost all such attempts, particularly in thrombocytopenic purpura, leukemia, Schönlein's purpura and hemophilia. Treatment of hemorrhagic states with vitamin C should not be carried out blindly but should depend on as clearcut evidence as possible that a deficiency of cevitamic acid exists.

Recognition, Frequency and Treatment of States of Vitamin C Deficiency.—The recognition of scurvy is not difficult, but determination of the presence of states of subclinical scurvy or hypovitaminosis C may be extremely difficult. Clinical features which might possibly lead to the suspicion that the disease is present include hemorrhagic tendencies, dental caries, spongy gums, abnormal cutaneous pigmentation, vague aches and pains, as well as fatigue, pallor, frequent infections, anemia and a history of an inadequate diet.

If suspicions are aroused, the next step to take in determining the presence of vitamin C deficiency is to perform the capillary resistance test (for technic, see Wright and Lilienfeld[103]). If the test shows a positive result, the evidence is suggestive but not conclusive. A negative test does not definitely exclude vitamin C deficiency. After this a therapeutic test, performed by administration of vitamin C orally or intravenously, with relief of symptoms or reversal of previously positive results of the capillary test, probably would be good evidence that the deficiency exists. Studies of the level of cevitamic acid in the blood and urine and the results of test doses give more objective evidence of the status of vitamin C nutrition (see foregoing section for details). However, normal values have not as yet been conclusively established.

The frequency of states of preclinical scurvy, or vitamin C hypovitaminosis, is unknown, but they are probably more common than previously was believed, particularly among members of the lower economic groups, among patients who have chronic infectious diseases and among those who are under prolonged and restricted dietary care. How frequently these states will be found among the general population will depend on observations in the future, based on standards as yet incompletely established.

103. Wright, I. S., and Lilienfeld, A.: Pharmacologic and Therapeutic Properties of Crystalline Vitamin C (Cevitamic Acid), with Especial Reference to Its Effects on Capillary Fragility, Arch. Int. Med. **57**:241-274 (Feb.) 1936.

The normal daily requirement of cevitamic acid of an adult is probably betwen 20 and 50 mg. Ordinary therapeutic doses are usually 200 mg. or less and may be given orally or intravenously. It is advocated by some to give to patients suspected of vitamin C deficiency 1,000 mg. daily for several days and thereafter to administer maintenance doses (30 to 50 mg.) with the idea of approaching saturation and of overcoming any tendency to deficiency which may exist.

VITAMIN D

Interest in vitamin D has been much increased because of the apparent multiplicity of substances which possess antirachitic properties. Because of variabilities in absorption and utilization of these substances by the same and different species of experimental animals, the difficulty of the problem has been multiplied. Further difficulties have arisen because of the variability in reports arising from the multiplicity of products formed by the irradiation of ergosterol. Bills [104] has presented evidence from chemical studies and bio-assays that at least eight distinct forms of the vitamin have been prepared by irradiation of materials containing provitamins. The three common sources of animal origin—fish liver oils, viosterol and irradiated milk—represent at least three chemically different vitamins D. From an extensive review of the literature Jeans [105] gave as his conclusion that vitamin D of animal source appears to be more potent for the use of man than vitamin D of vegetable source. Those interested in the chemical problems of vitamin D are referred to the excellent summaries of Bills [104] and McCollum.[106]

The mode of action of vitamin D is little understood. It is essential for adequate mineralization of bones and teeth and is therefore closely related to the metabolism of calcium, phosphorus and parathyroid hormone. Heymann [107] recently scrutinized this problem, particularly from the standpoint that vitamin D may act in a hormonal rôle in phosphate metabolism, as parathyroid hormone acts in calcium metabolism. He could find no evidence for such a hypothesis, although he found that vitamin D increased the diminished inorganic phosphate content of the

104. Bills, C. E.: New Forms and Sources of Vitamin D, J. A. M. A. **108**: 13-15 (Jan. 2) 1937.

105. Jeans, P. C.: Vitamin D Milk: The Relative Value of Different Varieties of Vitamin D Milk for Infants; a Critical Interpretative Review, J. A. M. A. **106**:2066-2069 (June 13); 2150-2159 (June 20) 1936.

106. McCollum, E. V.: The Fat-Soluble Vitamins, in Luck, J. M.: Annual Review of Biochemistry, Stanford University, Calif., Stanford University Press, 1936, vol. 5, pp. 379-402.

107. Heymann, W.: Studies on the Mode of Action and the Metabolism of Vitamin D, J. Pediat. **8**:480-488 (April) 1936.

blood in rickets. Nicolaysen,[108] in his study of the mode of action of vitamin D in rats, suggested that its action in phosphate metabolism is to increase the supply of phosphate from the intestinal contents to the blood stream and thence to the tissues. He could not produce evidence that it acted by maintaining a balance between the different forms of phosphorus in the organism. Warkany [109] recently has reported attempts at estimation of the vitamin D content of the blood serum. Using a method of bio-assay, he found that in man the values are from 45.9 to 135 U. S. P. units for each hundred cubic centimeters of serum, with an average value of 99.09 units. When rabbits were given by mouth 0.1 cc. of viosterol containing 100,000 U. S. P. units, there was elevation of the level of vitamin D in the serum in six hours. In twenty-four hours the maximal rise was present, amounting to about 2,700 U. S. P. units for one hundred cubic centimeters. This level was maintained for three or four days; it gradually became decreased, and normal levels were not attained until from four to six weeks later. During this period significant changes in phosphorus, calcium or phosphatase content of the serum were not noted.

There has been much controversy in recent years over the effectiveness of various therapeutic measures in the prevention of rickets and the healing of the lesions. Friedman,[110] in 1934, after an extensive review of the literature, pointed out, for example, that there is extensive clinical evidence to the effect that far fewer units of vitamin D in the form of milk containing vitamin D are required to protect against rickets or to heal rachitic lesions than are required with other antirachitic agents. This subject has been reviewed again this year (1936), for the Council on Foods of the American Medical Association, by Jeans; and with material made available from reports in recent years, he concluded that "such evidence as is available may be interpreted to show that cod liver oil, cod liver oil concentrate milk, and irradiated milk are of equal potency for the human being, unit for unit."

One source of error which may be overlooked by clinicians is the translation of results of work on the prevention of rickets and healing of rachitic lesions in rats and chickens to results obtainable in rickets of infants. No clearcut relation has been established among these groups. Massengale and Bills [111] explained that the conflicting reports

108. Nicolaysen, R.: Studies upon the Mode of Action of Vitamin D: I. Investigations upon the Phosphorus Compounds in Muscles, Liver and Kidneys as Influenced by Different Levels of Vitamin D and Phosphorus in the Diet, Biochem. J. **30**:1329-1337 (Aug.) 1936.

109. Warkany, Josef: Estimation of Vitamin D in Blood Serum, Am. J. Dis. Child. **52**:831-847 (Oct.) 1936.

110. Friedman, S.: Vitamin D Milk—a Résumé, J. Pediat. **4**:678-692 (May) 1934.

111. Massengale, O. N., and Bills, C. E.: A Quantitative Method for the Assay of Vitamin D with Chickens, J. Nutrition **12**:429-446 (Nov.) 1936.

on the relative effectiveness, rat unit for rat unit, of cod liver oil and viosterol for chicks lies in the fact that these materials are not broadly comparable. Their relative efficacy fluctuates with the degree of calcification: The difference is small at low calcification, one hundred times at "normal" calcification and great in production of extra hard bone.

Another source of error may be the frequency of administration and the dilution of the preparation that contains vitamin D, since absorption is undoubtedly an important factor. Lewis [112] has observed, for example, that in a group of 441 infants given vitamin D at three different levels (145, 290 and 1,450 units of crystalline vitamin D) in 28 ounces (840 cc.) of milk, in 7 drops of corn oil or in 7 drops of propylene glycol, rickets developed in those who received milk less frequently than in the others.

While the conclusion based on the work of many observers seems acceptable that, unit for unit, animal sources of vitamin D are essentially equal in antirachitic potency, there has been divergence of opinion in regard to the relative effectiveness of "yeast milk" (milk from cows fed irradiated yeast).

Evidence has been presented by Haman and Steenbock [113] that in the chick a distinct difference exists between the antirachitic activity of "yeast milk" and "irradiated milk." In fact, yeast milk was approximately a tenth as effective as irradiated milk. Bethke and his co-workers [114] obtained similar results. In a clinical study Davidson and his associates [115] reported that the feeding of yeast milk to premature infants as the sole source of vitamin D proved to be inadequate for achieving complete protection against rickets. As a result of his review, Jeans has concluded that, on the basis of unit for unit, yeast milk and viosterol milk are of the same value, that irradiated milk and cod liver oil concentrate milk are of the same value and that irradiated milk is superior to yeast milk, but on the basis of a difference probably not more than 1.5:1. This ratio is based entirely on curative experiments, and, as Jeans pointed out, corroboration by preventive experiments is highly desirable.

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112. Lewis, J. M.: Further Observations on the Comparative Antirachitic Value of Crystalline Vitamin D Administered in Milk, Corn, Oil, or in Propylene Glycol, J. Pediat. **8**:308-314 (March) 1936.

113. Haman, R. W., and Steenbock, H.: The Differential Antirachitic Activity of Vitamin D Milks, J. Nutrition **10**:653-666 (Dec.) 1935.

114. Bethke, R. M.; Krauss, W. E.; Record, P. R., and Wilder, O. H. M.: The Comparative Antirachitic Efficiency of Vitamin D in Irradiated Milk, Metabolized (Yeast) Milk, and Cod Liver Oil, J. Nutrition **11**:21-30 (Jan.) 1936.

115. Davidson, L. T.; Merritt, K. K., and Chipman, S. S.: Prophylaxis of Rickets in Premature Infants with Vitamin D Milk, Am. J. Dis. Child. **51**:1-16 (Jan.) 1936.

The constituent of milk which is important in increasing its antirachitic potency has been shown by Supplee and his associates [116] to be associated with the lactalbumin fraction.

Of greatest practical value in the problem of vitamin D is the dosage of the vitamin in the prophylaxis and treatment of rickets. In an excellent summary of their experience with viosterol over a period of six years at the Johns Hopkins Hospital, Shelling and Hopper [117] stated the conclusion that for full term infants a daily dose of 5 drops of viosterol, containing about 1,125 U. S. P. units, is efficacious in preventing rickets. For prematurely born infants and for babies growing at a too rapid rate, it may be advisable to administer from 15 to 20 drops of viosterol daily for the first three or four months of life and thereafter 5 drops, as for full term infants. In the treatment of rickets these workers employed doses of from 15 to 60 drops of viosterol daily, depending to some extent on the severity of the disease and the age of the infant or child. The average period required for healing was three and seven-tenths months. In groups receiving from 30 to 60 drops daily the average time for healing was not shortened, indicating that larger amounts than 20 drops of viosterol daily are not always more efficacious in inducing more rapid healing. Total refractoriness to viosterol was not encountered in the entire series, and partial refractoriness was noted in 1 case only. Toxic manifestations were never encountered, in spite of the fact that some children received viosterol in doses of from 30 to 60 drops daily for many months. Jeans concluded that animal-source vitamin D milk, with 135 U. S. P. units to the quart (1,000 cc.), will prevent rickets but that prevention of rickets is not a criterion of the adequacy of intake of vitamin D. He expressed the belief that animal-source vitamin D in the amount present in 1 standard teaspoonful of average high grade cod liver oil or in milk containing 400 U. S. P. units to the quart (1,000 cc.) is adequate for the infant from the standpoint of retention of calcium and growth. Beyond the age of infancy the exact requirement of vitamin D under any specified condition is unknown, but it appears to be increased during pregnancy and lactation.

The relation of diet, and particularly of vitamin D, to dental caries was emphasized in last year's review. Since that time a final report [118]

116. Supplee, G. C.; Ansbacher, S.; Bender, R. C., and Flanigan, G. E.: The Influence of Milk Constituents on the Effectiveness of Vitamin D, J. Biol. Chem. **114**:95-107 (May) 1936.

117. Shelling, D. H., and Hopper, Katherine B.: Calcium and Phosphorous Studies: XII. Six Years' Clinical Experience with Viosterol in the Prevention and Treatment of Rickets, Tetany, and Allied Diseases, Bull. Johns Hopkins Hosp. **58**:137-211 (March) 1936.

118. The Relation of Diet to Dental Caries, editorial, Lancet **2**:280-282 (Aug. 1) 1936. Diet and the Teeth, editorial, ibid. **2**:287-288 (Aug. 8) 1936.

of the Committee on Dental Disease, appointed by the Medical Research Council, in England, has been issued, entitled "Influence of Diet on Caries in Children's Teeth." Among the conclusions is the following statement:

> The investigations described in this report show conclusively that a relatively high vitamin D content of the food can do much to diminish the incidence of caries if the vitamin is given during the development of the teeth, that a beneficial effect may be obtained if the vitamin is given at a fairly late stage of development, and that even when it is given after the eruption of the teeth, the onset and spread of caries is delayed.

Concerning the series of 290 children carefully studied for a period of two and a half years, the committee reported that the addition of cod liver oil or vitamin D to the basal diet (which was a good one) reduced by half the incidence of caries in newly erupted teeth. To some extent a prophylactic effect was noted on previously erupted permanent and deciduous teeth.

The use of vitamin D to aid the healing of fractures has led to a variety of opinions, and conclusions will not be possible until further controlled work has been done. Deficiency of vitamins A and D or of vitamin D alone in the presence of experimental fractures in guinea-pigs leads to defective healing, principally because of defective formation of cartilage in the callus, according to Hertz,[119] who has provided an excellent summary of this problem.

The rôle of vitamin D in the metabolism of calcium and the relation among calcium, phosphorus, parathyroid hormone and vitamin D have not been clearly elucidated. In an interesting study of the etiology and diagnosis of hyperparathyroidism Wilder and Howell[120] stressed the important relation which has been shown to exist in experimental animals between insufficiency of vitamin D, on the one hand, and hyperplasia and hypertrophy of the parathyroid bodies, on the other hand. It is possible that vitamin D may be of some significance in the development or activation of adenoma of the parathyroid glands or in hyperplasia of these glands in man.

The use of large doses of vitamin D in cases of arthritis has been of considerable interest. Dreyer and Reed,[121] in a report of the progress in 280 unselected cases of arthritis, noted encouraging responses in many cases. Relief of pain, lessened disability and improvement

119. Hertz, John, quoted in Vitamins and the Healing of Fractures, editorial, Brit. M. J. **2**:980 (Nov. 14) 1936.

120. Wilder, R. M., and Howell, L. P.: Etiology and Diagnosis in Hyperparathyroidism: Review of One Hundred and Thirty-Five Proved Cases, J. A. M. A. **106**:427-431 (Feb. 8) 1936.

121. Dreyer, I., and Reed, C. I.: The Treatment of Arthritis with Massive Doses of Vitamin D, Arch. Phys. Therapy **16**:537-540 (Sept.) 1935.

in general condition were reported in relation both to infectious and to hypertrophic arthritis. On the other hand, the reports of Wyatt and his associates [122] and of Vrtiak and Lang [123] revealed results about commensurate with those of other types of treatment for arthritis. Dreyer and Reed used doses of 200,000 U. S. P. units daily and maximal doses of 300,000 units. Care must be taken to avoid toxic doses. The usual symptoms of toxicity are anorexia and gastrointestinal and urinary irritability. Occasionally persons apparently may be sensitive to vitamin D, for Thatcher [124] reported the case of a child given large, but not excessive, doses of vitamin D, who died apparently of vitamin D hypervitaminosis and who presented calcification in the kidney of sufficient degree to be noted at postmortem examination.

Recognition of States of Vitamin D Deficiency.—The diagnosis of well developed rickets is not difficult. In cases of mild involvement the most reliable method is roentgenologic examination of bones. Estimation of the phosphatase content of the serum also may be of value. For adults no definite criteria are available. Osteoporosis and changes in the levels of calcium and phosphorus in the serum may occur as a result of a variety of lesions involving calcium and phosphorus metabolism and the parathyroid bodies.

One might suspect vitamin D deficiency in patients with unusual or rapidly developing dental caries, osteoporosis, osteomalacia, tetany and insufficiently explained fractures. The condition is most likely to occur during pregnancy and lactation and in celiac disease, sprue and chronic jaundice.

VITAMIN E

Interest in the possible clinical significance of vitamin E has arisen because of reports in the literature regarding the use of wheat germ oil in the treatment of habitual and spontaneous abortion. Evans and his associates [125] have announced the isolation and have described the properties of an alcohol, α-tocopherol, which has the properties of vitamin E. Of 11 patients subject to habitual abortion (three to fifteen abortions) Watson [126] reported that 9 went to term and were

122. Wyatt, B. L.; Hicks, R. A., and Thompson, H. E.: Massive Doses of Vitamin D in the Treatment of Proliferative Arthritis, Ann. Int. Med. **10**:534-536 (Oct.) 1936.

123. Vrtiak, E. G., and Lang, R. S.: Observations on the Treatment of Chronic Arthritis with Vitamin D, J. A. M. A. **106**:1828 (May 23) 1936.

124. Thatcher, L.: Hypervitaminosis D, Lancet **1**:20-22 (Jan. 4) 1936.

125. Evans, H. M.; Emerson, O. H., and Emerson, G. A.: The Isolation from Wheat Germ Oil of Alcohol, α-Tocopherol, Having Properties of Vitamin E, J. Biol. Chem. **113**:319-332 (Feb.) 1936.

126. Watson, E. M.: Clinical Experiences with Wheat Germ Oil (Vitamin E), Canad. M. A. J. **34**:134-140 (Feb.) 1936.

delivered of normal children and that 6 of them completed pregnancy for the first time. Currie [127] also has reported good results. Just what the relationship may have been between habitual abortion and vitamin E deficiency in these cases is uncertain. The work of Rowlands and Singer [128] suggested that vitamin E helps to maintain the normal activity of the corpus luteum during early pregnancy, not by direct action but by stimulation of the gonadotropic functions of the pituitary body.

The Cooperative Committee of the Council on Pharmacy and Chemistry and of the Council on Foods, previously mentioned, has declared that there is no evidence to indicate that vitamin E has any therapeutic merit and has suggested that the Council on Foods refuse to accept any vitamin E preparation.

VITAMIN G (SEE VITAMIN B COMPLEX)

VITAMIN K

Considerable interest has been shown in the past year in the relation between hemorrhagic conditions and deficiency states. The importance of vitamin C has already been emphasized. That other factors may be significant was reported by Dam [129] in 1935, since he noted a hemorrhagic tendency resembling scurvy in chicks, not prevented by administration of cevitamic acid but produced apparently by a fat-soluble substance which he called vitamin K. Almquist and Stokstad [130] have reported that this vitamin is present in the fecal matter of chicks which are not receiving this factor in the diet and have expressed the belief that it is probably synthesized to some extent in the lower portion of the intestinal tract. The action of this substance, which occurs particularly in green vegetables, pig liver fat, hemp seed and alfalfa, most likely is attributable to the reduced content of prothrombin in the blood of chicks which are deficient in the substance, according to Dam and his associates [131] and to Schønheyder.[132] The clotting time can be restored to normal in three days by administration of

127. Currie, D. W.: Vitamins for Habitual Abortion, Brit. M. J. **1**:752 (April 11) 1936.

128. Rowlands, I. W., and Singer, E.: Gonadotropic Activity of the Pituitaries of Vitamin E Deficient Rats, J. Physiol. **86**:323-326 (March 9) 1936.

129. Dam, H.: The Antihaemorrhagic Vitamin of the Chick, Biochem. J. **29**: 1273-1285 (June) 1935.

130. Almquist, H. J., and Stokstad, E. L. R.: Factors Influencing the Incidence of Dietary Hemorrhagic Disease in Chicks, J. Nutrition **12**:329-335 (Oct.) 1936.

131. Dam, Henrik; Schønheyder, Fritz, and Tage-Hansen, Erik: Studies on the Mode of Action of Vitamin K, Biochem. J. **30**:1075-1079 (June) 1936.

132. Schønheyder, Fritz: The Quantitative Determination of Vitamin K, Biochem. J. **30**:890-896 (May) 1936.

the substance in which the animal is deficient. In rabbits Quick [133] has produced a hemorrhagic tendency with reduction of prothrombin by feeding spoiled sweet clover hay. He has expressed the belief that such hay contains a toxic substance which either destroys prothrombin or inhibits the mechanism by which the body produces this clotting factor and that alfalfa exerts a curative effect by supplying an accessory factor not identical with, but possibly related to, vitamin K and required by the organism for synthesis of prothrombin.

The importance to man of vitamin K, or of the related factor reported by Quick, has not been noted. Attention should be directed toward the possible rôle of these factors in the hemorrhagic tendencies of man.

THE OCCURRENCE OF OTHER ESSENTIAL FOODSTUFFS

Each year sees the reports of substances considered essential for normal nutrition and not included in the present list of vitamins or minerals. Two such reports in the past year suggested new dietary essentials. Elvehjem and his collaborators [134] in their experiments with rats identified a water-soluble, heat-labile factor, now called "alcohol-ether precipitate factor," distinct from any of the known dietary essentials. In the absence of this factor complete failure of growth of rats results, and the authors expressed the belief that this factor may explain the difficulty which previously has been encountered in the use of synthetic rations. A fat-soluble substance has been found by Goettsch and Pappenheimer [135] to be essential for chicks; they have found that absence of this substance leads to lesions of the nervous system. While the deficiency state produced is similar to that resulting from absence of vitamin B_4, this new factor is fat soluble, whereas vitamin B_4 is water soluble.

Zinc.—Evidence that zinc is indispensable for rats has been demonstrated by Elvehjem and his colleagues.[136] Lack of this metal leads to retardation of growth and interference with development of a normal coat of hair. In man the only definitely known relationship of zinc to health is in its relation to the prolongation of action of insulin.

Iron.—Anemia attributable to nutritional deficiency of iron is of common occurrence. Murphy [137] has emphasized the fact that hypo-

133. Quick, A. J.: The Coagulation Defect in Sweet Clover Disease and the Hemorrhagic Chick Disease of Dietary Origin, Am. J. Physiol., to be published.

134. Elvehjem, C. A.; Koehn, C. J., Jr., and Oleson, J. J.: A New Essential Dietary Factor, J. Biol. Chem. **115**:707-719 (Oct.) 1936.

135. Goettsch, Marrianne, and Pappenheimer, A. M.: A New-Found Diet Factor, Science (supp.) **84**:7 (Aug. 28) 1936.

136. Elvehjem, C. A., and others, cited in Nutritional Significance of Zinc, editorial, J. A. M. A. **106**:1011-1012 (March 21) 1936.

137. Murphy, W. P.: Deficiency States—Anemia, J. Am. Dietet. A. **11**:406-410 (Jan.) 1936.

chromic anemias are true deficiency diseases and are attributable to an inadequate supply or inadequate utilization of iron. This may come about as a result of loss of iron, as in cases of chronic hemorrhage; from insufficient intake or absorption, or from unsatisfactory utilization, about which little is understood.

In their studies of the utilization of iron in experimental anemia of dogs, Whipple and Robscheit-Robbins [138] have come to the conclusion that iron given intravenously will return quantitatively as newly formed hemoglobin on the basis of 10 mg. of iron for 3 Gm. of hemoglobin. The influence of iron when given by mouth on production of hemoglobin is not proportional to the dose. The optimal dose of iron (40 mg. per day for two weeks, or 560 mg.) gives a return of about 55 Gm. of hemoglobin and amounts to 35 per cent utilization. With larger doses of iron, for example, 400 mg. daily, the daily output of about 95 Gm. of hemoglobin represents about 5 per cent utilization. These observers found that iron salts are utilized with equal facility by the dog to produce hemoglobin when given by mouth in the ferrous, ferric or reduced state. The determining factor is the amount of metallic iron. Interesting studies on the absorption of iron in the dog have led Scheunert and Brüggemann [139] to the conclusion that reduced iron is absorbed better than is iron in colloidal form. In their dogs with ileal fistulas they found that more than 66 per cent of the iron given in various preparations was usually absorbed.

Interference with absorption of iron by some patients who have achlorhydria has been known to be a cause of hypochromic anemia. Apparently the hydrochloric acid in gastric juice is an important aid in absorption of iron. In this connection the studies of Kellogg and Mettier,[140] on the effect of alkaline therapy in relation to utilization of dietary iron and to regeneration of hemoglobin in cases of peptic ulcer, are worthy of note. While they studied only a small number of patients, the results indicated clearly that the bone marrow of patients undergoing alkaline therapy failed to respond to the ingestion of dietary iron as determined by production of hemoglobin. When the alkaline regimen was discontinued, increase in the concentration of hemoglobin occurred. In contrast, increase in the number of erythrocytes and reticulocytes occurred soon after the addition of iron-rich diets to the alkaline regimen. The likely conclusion is that alkalini-

138. Whipple, G. H., and Robscheit-Robbins, F. S.: Iron and Its Utilization in Experimental Anemia, Am. J. M. Sc. **191**:11-24 (Jan.) 1936.

139. Scheunert, A., and Brüggemann, J.: Ueber Eisenresorption bei Ileumfistelhunden, Nutrition Abstr. & Rev. **5**:1031-1032 (April) 1936.

140 Kellogg, F., and Mettier, S. R.: Effect of Alkaline Therapy for Peptic Ulcer on Utilization of Dietary Iron in the Regeneration of Hemoglobin, Arch. Int. Med. **58**:278-284 (Aug.) 1936.

zation of the upper part of the gastro-intestinal tract interferes with utilization of dietary iron for the synthesis of hemoglobin but not with the utilization of material necessary for the formation of the stroma of erythrocytes.

The success with which iron can be used in the prevention of hypochromic anemia during pregnancy is suggested by the observations on 200 women during the last four months of pregnancy by Corrigan and Strauss.[141] Twenty-four of 100 patients to whom iron was not given had values for hemoglobin of less than 70 per cent post partum. On the other hand, none of the 100 women who received 0.5 Gm. of ferrous sulfate daily during the last four months of pregnancy had less than 70 per cent of hemoglobin post partum.

PREGNANCY AND LACTATION

In an interesting review of recent work on dietetics in which the attempt was made to correlate and assess requirements for various dietary essentials during pregnancy and lactation, Garry and Stiven[142] pointed out certain conclusions which should be of practical value in the future. It was clearly emphasized that present knowledge does not permit categorical statement of the amounts of the various dietary essentials which are required for correct nutrition during these periods of physiologic activity. General principles are still the guide-posts. However, standards have been set by the League of Nations Health Committee (Technical Commission);[143] and although these standards are high, they are probably necessary, and, as the authors pointed out, the evidence from dietary surveys indicates that many dietaries may fall far below these standards. Since during pregnancy and lactation the maternal organism is subjected to special demands which, in a sense, may be considered efficiency tests, it seemed logical to Garry and Stiven that dietary deficiencies in a population are likely to be evidenced more clearly among pregnant and nursing women than among the general adult population. From the practical standpoint, as McIlroy[144] has intimated, the real solution lies in the kitchen rather than in the laboratory or hospital ward.

The collected data indicate that under ordinary circumstances diet has little effect on birth weight; this seems to depend more on the

141. Corrigan, J. C., and Strauss, M. B.: The Prevention of Hypochromic Anemia in Pregnancy, J. A. M. A. **106**:1088-1090 (March 28) 1936.

142. Garry, R. C., and Stiven, D.: A Review of Recent Work on Dietary Requirements in Pregnancy and Lactation, with an Attempt to Assess Human Requirements, Nutrition Abst. & Rev. **5**:855-887 (April) 1936.

143. Technical Commissioner's Report on Physiological Bases of Nutrition, League of Nations Health Committee, quoted by Garry and Stiven.[142]

144. McIlroy, L., and others: Discussion on Diet in Pregnancy, Proc. Roy. Soc. Med. **28**:1385-1406 (Aug.) 1935.

growth impulse of the child and on the mother's constitution than on the mother's intake of food. Little information is available about the effect of variation in protein content of the diet in pregnancy. The impression seems to be general that excess of proteins, or of particular proteins, is harmful, and restriction of intake of meat is advised rather widely during pregnancy, Strauss [145] has produced evidence that a diet low in protein may in some cases be the cause of toxemia of pregnancy. He has reported successful treatment in some cases with a diet high in protein supplemented by vitamin B_1 and liver. The Technical Commission (League of Nations) has advised an intake of protein during pregnancy of 2 Gm. for each kilogram of body weight, which seems high, in the early stages of pregnancy. The requirement of iron during pregnancy is variable. A variety of factors, such as vomiting and interference with absorption from hypoacidity, may alter the requirement. Macy and Hunscher [146] estimated the desirable intake as 20 mg. of iron a day, and Coons and Coons [147] discovered that the addition of wheat germ to a diet already providing 20 mg. of iron a day greatly increased the storage of iron. The League of Nations (Technical Commission) has recommended the use of 1 quart (1,000 cc.) of milk daily to satisfy the calcium requirement of the pregnant woman. For lactating women the commission has recommended 2 Gm. of calcium daily. The requirement for vitamins is difficult to establish, but the commission has recommended 9,000 U. S. P. units of vitamin A, from 150 to 250 international units of vitamin B, from 870 to 1,120 international units of vitamin C and 340 U. S. P. units of vitamin D both during pregnancy and during lactation.

THE FREQUENCY, RECOGNITION AND TREATMENT OF DEFICIENCY STATES

In the review last year [60] some of the interesting phases having to do with the problem of nutrition of the people as a whole were discussed with particular reference to malnutrition, the influence of the economic depression on dietary habits and intake and the potentialities of an adequate diet with reference to the individual and the

145. Strauss, M. G.: Observations on the Etiology of the Toxemias of Pregnancy: Relationship of Nutritional Deficiency, Hypoproteinemia, and Elevated Venous Pressure to Water Retention in Pregnancy, Am. J. M. Sc. **190**:811-824 (Dec.) 1935.

146. Macy, I. G., and Hunscher, H. A.: An Evaluation of Maternal Nitrogen and Mineral Needs During Embryonic and Infant Development, Am. J. Obst. & Gynec. **27**: 878-888 (June) 1934.

147. Coons, C. M., and Coons, R. R.: Some Effects of Cod Liver Oil and Wheat Germ on the Retention of Iron, Nitrogen, Phosphorus, Calcium and Magnesium During Human Pregnancy, J. Nutrition **10**:289-310 (Sept.) 1935.

race. As knowledge advances a much clearer conception is being gained of the qualitative and quantitative dietary requirements of man. However, the problem is a much greater one than simply an understanding of such requirements, for, as was pointed out in a recent interim report of a League of Nations committee,[148] agricultural, economic and health aspects are equally important. It is stated that "the evidence that inadequacy of diet is widespread is conclusive, malnutrition is manifest in prevalence of rickets, scurvy, poor musculature, teeth of poor structure, anemia, chronic fatigue, poor condition of the skin, and subnormal growth and weight to mention the most easily observable symptoms." Emphasis is placed on the well known fact that protective vitamin-containing foods are expensive and, therefore, from the economic standpoint the greatest single cause of defective nutrition is poverty. The importance of nutrition as a part of medicine is clearly demonstrated by the establishment of a section of nutrition by the British Medical Association.

The influence of the depression on the nutrition of the American people has been analyzed recently by McLester.[149] He has approached the problem from the standpoint of "(*a*) the weight and the increment of gain among school children, as recorded before and after the depression; (*b*) the weights of the employed and unemployed among working men together with estimates of fitness; (*c*) the testimony of welfare agencies, and (*d*) the clinical observations of a selected group of physicians." He expressed the belief that, on the whole, the figures suggested that the nutritive state of the American school child has not suffered during the depression and that there has been no widespread undernutrition among the general population. The incidence of deficiency diseases, as observed by a group of clinicians throughout the country, shows slight if any increase, with the possible exception of a few areas. McLester expressed the belief that these good results are largely attributable to education.

While it seems evident that the incidence of clearly recognizable deficiency states has not increased appreciably, there has been much discussion of the incidence of occurrence of partial deficiencies, the diagnosis of which depends in large part on keen and critical observations, on chemical or pathologic studies and on other laboratory methods. Minot[150] expressed the belief that such borderline states of nutritional instability are more common than usually is appreciated, since there is a wide zone between optimal nutrition and the level

148. The Problems of Nutrition, editorial, Brit. M. J. **2**:396 (Aug. 22) 1936.

149. McLester, J. S.: Influence of the Depression on the Nutrition of the American People, J. A. M. A. **106**:1865-1869 (May 30) 1936.

150. Minot, G. R.: Nutrition and Deficiency Disease, New York Times, Sept. 15, 1936.

at which classic symptoms of recognized deficiency states develop. The use of chemical methods, particularly of those which permit estimation of the vitamin content of the urine, blood and other tissues, opens up an entirely new field in the recognition of deficiency states, although interpretation of results is still of questionable diagnostic significance.

In each section earlier in this review note has been made of methods of recognizing specific deficiency states. It is important to remember that deficiency states may occur alone or in association with other diseases, that a carefully taken dietary history may be of considerable value and that, with the use of pure preparations of vitamins, a therapeutic trial may aid in establishing the diagnosis.

In his efforts to recognize deficiency states the clinician must pay particular attention to the types of patients who may be expected to suffer from such conditions. Deficiencies may result from a variety of causes other than an inadequate diet. All the following factors may be significant in predisposing to deficiency: increased requirements during periods of rapid growth, pregnancy, infections and fever and when the metabolic rate is elevated; loss of abnormal quantities of essential substances (for example, by vomiting or diarrhea); impaired or altered gastro-intestinal function, and alteration in the metabolism of the vitamins (for example, in storage, destruction and utilization). Of these various factors, the most important from the standpoint of frequency are a diet that is inadequate because of poverty, because of faddism or, at times, because of treatment of disease and alteration in gastro-intestinal function (see the following comment).

In the treatment of deficiency states the most important factor is a well balanced, adequate diet which can be supplemented when necessary by preparations containing vitamins in concentrated form. Too much emphasis cannot be placed on the value of giving vitamins in a natural state. This is particularly true in relation to components of the vitamin B complex. Crystalline preparations of vitamin B_1 are of undoubted value in specific conditions, but because of the uncertainty of the number of components of the vitamin B complex which are necessary for normal health, it seems wise to supplement in most cases, and except under conditions of experiment, the administration of the crystalline product with preparations such as brewers' yeast or wheat germ, which contain all the essential components.

If vitamin preparations can be successfully given orally, this seems the most desirable method of administration because it approaches the normal. Intramuscular and intravenous routes of administration have given more rapid response in some cases. The minimal require-

ment of each vitamin has not been clearly established, and experience has shown the wide zone which may exist between minimal and optimal requirements. Optimal levels are probably ideal levels. For therapeutic purposes, doses much larger than optimal requirements may be used. So far as is known, vitamin D is the only vitamin which in large doses can produce toxic effects.

Vitamin A can be administered in a variety of foods, either those which contain the elements in the form of the vitamin or as carotene. Carotene is not as well absorbed as vitamin A, and consequently in most circumstances the vitamin is the more satisfactory preparation to use. Preparations of vitamin A for parenteral use have not proved satisfactory, but crystalline carotene can be used as a substitute. Fish liver oils, particularly those of the halibut, cod and burbot, are rich sources of vitamin A for therapeutic use.

The vitamin B complex can be given in the form of brewers' yeast or wheat germ. Concentrates of vitamin B_1; liver extract, which is high in vitamin B_2 (G) content, and crystalline vitamin B_1 (now synthetically prepared) are all useful. The crystalline preparation can be used parenterally in therapeutic doses of from 10 to 20 mg. daily. In the treatment of pellagra Spies [151] has emphasized the importance of giving large doses of yeast or wheat germ and has recommended from 75 to 100 Gm. daily.

Vitamin C can be given in the form of citrus fruit or tomato juice or in crystalline preparations by mouth or intravenously. The daily requirement lies probably between 30 and 50 mg., and therapeutic doses range from 50 to 200 mg. daily.

For the child the Council on Foods of the American Medical Association recommends the daily use of 2 teaspoonfuls of cod liver oil (N. N. R., 1936) for a satisfactory intake of vitamins D and A. Irradiated milk, viosterol and irradiation of the skin are all good therapeutic sources of vitamin D. For dosages reference may be made to the articles of Jeans and of Shelling and Hopper. The Council on Pharmacy and Chemistry of the American Medical Association [152] has taken a firm stand against the use of "shotgun vitamin therapy." Absence of evidence of the value and safety of such preparations and the frequent lack of necessity of taking them are emphasized. Shoddy diagnosis and treatment of actual and suspected deficiency disease should, by all means, be avoided if rapid and clearcut progress is to be made in this important field.

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151. Spies, T. D.: Treatment of Pellagra, J. A. M. A. **104**:1377-1380 (April 20) 1935.

152. Shotgun Vitamin Therapy, report of Council on Pharmacy and Chemistry, J. A. M. A. **105**:1037-1038 (Sept. 28) 1935.

THE GASTRO-INTESTINAL TRACT IN RELATION TO DEFICIENCY DISEASES

The relationship between gastro-intestinal disturbances and deficiency states may be a reciprocal one. It has been clearly established that abnormalities of the tract may lead to deficiency states, and it is equally certain that deficiency states may lead to pathologic changes in the gastro-intestinal tract. Under certain conditions it is not clear which of the two comes first in a given case or whether they may be independent parts of the clinical picture.

Alterations in gastro-intestinal function which may produce a deficiency state have been classified by Wilbur and Snell [153] as follows: (1) inadequate intake of food (attributable to anorexia, incomplete diet and so forth); (2) loss of essential secretions or of food (attributable to vomiting, diarrhea or external fistula); (3) lack or decreased production of essential substances (for example, of hematopoietic factors, bile and digestive juices), and (4) inadequate intestinal absorption (attributable to obstruction, short-circuiting produced by a gastro-intestinal fistula, atrophy or disease of the intestinal mucosa).

Numerous cases illustrating these points have been reported in the past year. Perhaps the most interesting have to do with the influence of lack of bile on the absorption of vitamin A (see section on vitamin A). Bissell and Andrews [154] have made extensive studies of acholic cachexia in dogs and have reported that anemia, osteoporosis and gastroduodenal ulceration did not develop. The lives of the dogs were not prolonged by subcutaneous administration of vitamin D. The investigators concluded that acholic cachexia is not attributable to absence of bile from the intestinal tract, with consequent inability to absorb any specific food or vitamins. Klodt expressed the belief that bile facilitates absorption of vitamin C in the small bowel by considerably retarding oxidation of dilute solutions of vitamin C.

The effect of achlorhydria on gastro-intestinal function has been widely explored. In the past year Einhauser has pointed out that utilization of test doses of vitamin C by patients with achlorhydria is disturbed because of inadequate absorption. With Schroeder he reported a case of pernicious anemia with pigmentation of the face unaffected by treatment for pernicious anemia but promptly corrected by 300 mg. of cevitamic acid given intravenously each day for fourteen days.

There has been much discussion of the effects on the gastro-intestinal tract of deficiency states. Much of the work reported has

153. Wilbur, D. L., and Snell, A. M.: Unpublished data.

154. Bissell, A. D., and Andrews, E.: Acholic Cachexia: Experimental Studies, Arch. Surg. **32**:624-668 (April) 1936.

been based on animal experiments. Attempts to prove nutritional deficiency as an etiologic factor of such conditions as peptic ulcer generally have met with failure. Hurst [155] stated that he had never found any evidence for a nutritional origin of a gastro-intestinal disease in England. Stepp [156] gave the opinion that deficiency of vitamin A may lead to a reduced hydrochloric acid content of gastric juice, interference with absorption and diarrhea. McCarrison [157] expressed the belief that vitamin A deficiency leads to infections in the digestive tract. A summary of the effect of deprivation of vitamin A on the gastro-intestinal tract was presented by Robertson.[158] The close relationship which may exist between components of the vitamin B complex and digestive function is illustrated by the accompanying atrophy of the papillae of the tongue, anorexia, achlorhydria and hypotonicity and hypomotility of the musculature, particularly of the small intestine. In a study of the effect of vitamin B_1 deficiency on the gastric juice of 2 healthy subjects, Alvarez and his co-workers did not find definite changes in concentration of hydrochloric acid or pepsin after six weeks (vitamin-calory ratio of 1.2 instead of Cowgill's minimum normal of 1.8). Villaret and his associates,[159] in their study of the character of gastric disorders in the course of alcoholic polyneuritis, found achlorhydria and hypochlorhydria with atrophic gastritis to be not uncommon. Improvement in these abnormalities preceded improvement of the neuritis after treatment was instituted. In rats Simpson could not find atrophy, ulceration or erosion of the gastric mucous membrane in vitamin B_1 deficiency. He expressed the belief that many of the variable reports in the literature are attributable to lack of uniformity in choice of animals and in dietary standards. Changes in enzymes which may accompany vitamin B deficiency have been incompletely studied. Kik, Sure and Buchanan have noted interesting changes which have been reported previously in this review (see section on vitamin B complex). Little is known of the effect of vitamin B_2 (G) deficiency on the intestinal tract, although the presence of the vitamin is thought to be necessary to maintain the mucosa in normal condition. Absence of vitamin C was reported by McCarrison to lead to congestion, hemorrhage and ulcerating lesions.

155. Hurst, A. F., quoted in discussion on Nutrition in Health and Disease, Lancet **2**:260-262 (Aug. 1) 1936.

156. Stepp, W.: Vitaminmangel als Ursache und Folge von Magen-Darmerkrankungen, München. med. Wchnschr. **83**:1119-1123 (July 10) 1936.

157. McCarrison, Robert: Nutrition in Health and Disease, Brit. M. J. **2**:611-615 (Sept. 26) 1936.

158. Robertson, Elizabeth C.: Recent Work on the Tissue Changes in Vitamin "A" Deficiency, Am. J. M. Sc. **192**:409-436 (Sept.) 1936.

159. Villaret, M.; Moutier, F.; Justin-Besançon, L., and Klotz, H. P.: Special Character of Gastric Disorders in Course of Grain Alcohol Polyneuritis, abstr., J. A. M. A. **107**:1346 (Oct. 17) 1936.

The remarkable effect of liver extract on hematopoietic function constitutes the outstanding therapeutic value of this substance in pernicious and other macrocytic anemias. That substances in liver extract may influence also gastro-intestinal function has not been well recognized. In a recent report Jones, Benedict and Hampton [160] noted the gastroscopic, surgical and roentgenologic observations which they made in a group of 5 patients with pernicious anemia. Following successful specific therapy of pernicious anemia, evidence of atrophy or hypertrophy of the gastric mucosa tended to disappear; Jones, Benedict and Hampton expressed the belief that this effect was attributable not only to increased blood supply but also to epithelial change associated with successful treatment of a specific deficiency state, rather than to healing of a chronic inflammatory process. In an equally interesting paper, Miller and Rhoads [161] reported studies of the small intestine of a patient who had sprue without anemia. Following injection of liver extract there was a return toward normal form and function of the intestine, as was evidenced by roentgenologic study as well as disappearance of symptoms. It is suggested that liver extract administered parenterally conditions the functional activity of the small intestine. These reports are of particular interest because they tend to substantiate the belief of some workers that a close relationship exists between the hematopoietic factor of pernicious anemia and a factor similar to vitamin B_6 but that the two are not identical.

The oral complications of chronic alcoholism which may be wholly or in part of nutritional origin have been discussed by Blankenhorn and Spies and have been noted previously in this review.

Although knowledge of intestinal absorption is still meager, attention is called to studies noted previously in the review which have to do with absorption of carotene, interference with absorption of vitamin A in pregnancy, absorption of vitamin B_1 in dogs, absorption of vitamin D administered to infants in a variety of mediums and absorption of iron, particularly as it may be influenced by simultaneous administration of alkalis. Interference with absorption of vitamin C in achlorhydria also has been noted.

In experimental work Irwin, Steenbock and Kemmerer [162] have observed that rats with avitaminosis (from lack of vitamins A, B

160. Jones, C. M.; Benedict, E. B., and Hampton, A. O.: Variations in the Gastric Mucosa in Pernicious Anemia: Gastroscopic, Surgical and Roentgenologic Observations, Am. J. M. Sc. **190**:596-610 (Nov.) 1935.

161. Miller, D. K., and Rhoads, C. P.: The Effect of Liver Extract on the Small Intestine of Patients with Sprue, Am. J. M. Sc. **191**:453-456 (April) 1936.

162. Irwin, Margaret H.; Steenbock, H., and Kemmerer, A. R.: The Influence of Vitamins A, B, or D, Anemia or Fasting upon the Rate of Fat Absorption in the Rat, J. Nutrition **12**:357-364 (Oct. 10) 1936.

or D) absorbed fat less rapidly than normal, but this was interpreted as a nonspecific effect. The addition of these vitamins to the diet of normal rats did not increase their ability to absorb fats.

Attention should be called to interesting studies which have been made on the nature and relationship of sprue, idiopathic steatorrhea, celiac disease and pernicious anemia. There is still much disagreement as to the nature of the intestinal, histopathologic and physiologic changes in these diseases. It is not possible to discuss in detail all the evidence which has been presented in this controversy, and it is suggested that reference be made to the original articles. Castle and his associates,[163] in an excellent study of 90 patients with sprue observed in Puerto Rico and Boston, pointed out that sprue, pernicious anemia and pellagra have many similar features, especially as regards the blood, gastro-intestinal system and nervous system. They suggested that sprue is a deficiency disease closely related to pernicious anemia and that lack of intrinsic or extrinsic factors or failure of absorption of them is a significant etiologic factor. Deficiency of iron in the diet also may be a factor.

On the other hand, Fairley,[164] who has studied 450 patients with tropical sprue in London and elsewhere throughout the world, expressed the belief that the disease is essentially different from pernicious anemia, celiac disease and idiopathic steatorrhea. He found sprue to affect many well-to-do persons who had been on an adequate diet, and he observed at postmortem examination no specific degeneration or inflammatory change in the intestine. He expressed the opinion that the phenomena of tropical sprue may best be explained in terms of a metabolic breakdown of the gastro-intestinal tract, characterized by defective absorption in the small intestine, with or without defective secretion of Castle's intrinsic factor. There is marked failure to absorb fat and often dextrose; moreover avitaminosis, when it occurs, is a secondary phenomenon dependent on malabsorption or on a too restricted diet, self-imposed with the object of cure. The disease responds to limitation of fat and administration of calcium without vitamin D. Further evidence of impairment of carbohydrate metabolism in celiac disease has been presented by Ross,[165] who has shown that liver extract may significantly influence carbohydrate metabolism by a factor possibly identical with Himsworth's "insulin-kinase."

163. Castle, W. B.; Rhoads, C. P.; Lawson, H. S., and Payne, G. C.: Etiology and Treatment of Sprue, Arch. Int. Med. **56**:627-699 (Oct.) 1935.

164. Fairley, N. H.: Tropical Sprue with Special Reference to the Intestinal Absorption, Tr. Roy. Soc. Trop. Med. & Hyg. **30**:9-32 (June) 1936.

165. Ross, C. W.: Intestinal Aborption in Coeliac Disease, with Some Remarks on the Effect of Liver Extracts upon Carbohydrate Metabolism, Tr. Roy. Soc. Trop. Med. & Hyg. **30**:33-50 (June) 1936.

Book Reviews

Röntgenkymographische Bewegungslehre innerer Organe. By Pleikart Stumpf, M.D., H. H. Weber, M.D., and G. A. Leltz, M.D. Price, 42 marks. Pp. 516, with 447 illustrations and 1 celluloid grid. Leipzig: Georg Thieme, 1936.

This book was written mostly by Stumpf; in other words, he was not merely the editor. In the first 43 pages he takes up a discussion of what roentgen kymography is, the methods of using it and the apparatus for taking kymograms and for viewing and measuring them. He measures not only outlines but also variations in density, so that a time curve of the alteration of the thickness of an organ may be obtained. He explains the distinction between surface kymography made with the grid moving and staircase kymography made with the film moving. He points out that each method has its uses. The rest of the book is taken up with a discussion of the uses of kymography for diagnosis in various parts of the body.

There are about 120 pages devoted to the heart in health and disease, and the movements of the heart are analyzed with regard to time and extent. Many of Stumpf's kymographs are timed by electrocardiograms. He gives statistical averages for various chambers for various ages. He also considers the effect of respiration.

One chapter is devoted to the shape of the kymographic curve for various disease conditions, and an explanation is given for each form. However, on the whole the chapter seems empirical rather than theoretical, and it appears to be extremely practical.

There is a 10 page chapter on the pulsations transmitted to other organs than the chest, and then Weltz gives 30 pages on the thoracic aorta, which he considers a mere beginning of the study. He also goes further into the matter of the effect of respiration on the movement of the heart. This chapter overlaps somewhat a briefer discussion by Stumpf on pages 81 to 88.

Bohme gives 20 pages on a most interesting study, mostly experimental studies on animals, of the movements of the chambers and vessels and of the blood within them. The demonstration was made by the injection of colloidal thorium diiodide and sometimes iodized poppy-seed oil into the blood stream. It seems to me that this is a valuable method for investigations in physiology.

Weber gives 35 pages of discussion on the movements of the diaphragm, ribs, lobes of the lungs and bronchi in normal respiration.

Weltz contributes a 20 page discussion of pathologic respiration, especially in asthma.

Dong devotes 50 pages to respiration in the presence of disturbed musculature or innervation and in the presence of tumors of the lungs. I received the impression that this field of clinical investigation is difficult. It is hard for me to evaluate which of his results may be clinically useful and which are only interesting demonstrations of the roentgen kymograph. Disturbances by infiltrations and by interlobar pleural adhesions can be brought out in this and apparently in no other way.

Von der Weth gives a 32 page report on alterations in the breathing mechanism in pulmonary tuberculosis. It seems possible that this information, attainable by no other method than roentgen kymography, may be of great importance as a guide to therapy, for instance, by showing the effect of interlobar adhesions in transmitting diaphragmatic movement into the upper lobe of the lung. The demonstration of such an effect in a patient might easily be the determining consideration in deciding on section of the phrenic nerve.

There are 13 pages by Schoen on substernal goiter alone.

The alimentary tract receives only 80 pages. I expect that this section will be considerably expanded in the future, although in this region, where movements are usually slow enough to be followed with the eye on the fluoroscopic screen,

I do not know how essential kymography may become for diagnostic purposes. There is a 24 page chapter by Dahm on the esophagus. The rest of the discussion of the stomach and duodenum is by Stumpf himself. The analysis of peristaltic movements from roentgen kymograms is necessarily carried out in detail, for here where the movement consists of a peristaltic wave passing over a long organ, it is not as easy to recognize its true nature by means of a kymogram as it is in the case of the heart, where the pulsation is more of the organ as a whole.

Stumpf's discussions of the stomach and duodenum contain a good deal of investigation of normal physiology. This is, of course, absolutely essential as a background for understanding any pathologic disturbance of motility. It is still difficult to analyze the effects of the muscular coats and of the muscularis mucosae.

Twenty-five pages by Sack cover the urinary tract. Peristaltic movement in the ureter is beautifully demonstrated.

There is a closing chapter of 6 pages by Neeff in which he discusses the dangers from the heavy intensity of irradiation necessary to produce roentgen kymograms. These exposures fall well within the limits of what is safe. Nevertheless, if the ovaries or testes are in the field, a single roentgen kymogram might under some circumstances be as large an exposure as should ordinarily be undertaken, i. e., one should not advise a repetition of the examination. In the chest there is much more leeway, so that a good many roentgen kymograms can be taken of the heart and lungs without treading on ground that is at all dangerous.

On Deficiency of A Vitamin and Visual Dysaptation. By C. Edmund and S. Clemmesen. Price, 5 kroner. Pp. 92. Copenhagen: Levin & Munksgaard, 1936.

A considerable portion of the principal essay in this brochure is devoted to a detailed and critical study of the method employed for the determination of the power of distinction and its use in the detection of visual dysaptation (nyctalohemeralopia). Using various Tscherning neutral filters and a series of Snellen letters (6/36) of different shades of gray, with Bouguer-Fechner fractions varying in geometric progression, these investigators determined the power of distinction (logarithm of the reciprocal value of the B-F fraction) at different levels of illumination for groups of hospital nurses, pregnant women, and male and female patients selected at random. Details are presented regarding the determination of correct B-F fractions represented by the gray letters used in order that powers of distinction may be indicated in absolute values, thereby making possible a comparison of the results of various investigators. A number of pages are devoted to the experimental technic, errors of the method, determination of the normal curve and limits of normal zone, seasonal variations and the influence of age.

The ensemble of apparatus and methods used by the authors are suitable and doubtless adequate for clinical investigations. Obviously, the findings by such methods are not to be regarded as determinations of the threshold of sensitivity to light, in which the foveal and peripheral retinal perception of light and the effects of adaptation may be determined. However, investigations by others indicate a reduction in function of the central parts of the retina as well as of the periphery for white and colored light in hemeralopia. To a certain extent visual acuity enters into the findings obtained by Edmund and Clemmesen and may give powers of distinction which are too low. In general, determinations of the minimum visible, examinations of visual fields at reduced illumination and determinations of visual acuity under reduced illumination are somewhat unsatisfactory clinically, since they tax the intelligence of the patient or are not sufficiently sensitive to detect slight hemeralopia. In certain respects, therefore, the determination of the power of distinction is the method of choice, since the estimation of how great the differences in brightness must be in order to be noticed is of importance in daily life.

The concluding portion of the essay and the appended article on the parenteral treatment with vitamin A of dysaptation (nyctalohemeralopia) in some pregnant women give details of treatment and tables of data regarding the power of distinction before and after the administration of vitamin A. A group of fifty-two

nurses in the Sundby Hospital, Copenhagen, were found to be normal in power of distinction, with a marked tendency to the lower limit of normalcy during the winter months. A preventive diet containing from 1,500 to 2,000 U. S. P. units of vitamin A is suggested and emphasis is laid on the inclusion of sufficient vegetables in the diet during the winter months. Nearly half the forty-nine pregnant women tested for dysaptation showed a pathologic decrease in the power of distinction. Intramuscular injections of a vitamin A preparation (containing about 40,000 U. S. P. units) produced a disappearance of dysaptation which lasted for about a week in the majority of cases. In general these investigations showed the correlation between vitamin A deficiency and reduction in the power of distinction and demonstrated the improvement of function produced by the administration of the vitamin.

Applied Dietetics for Adults and Children in Health and Disease. By Sanford Blum, M.D. Price, $4.75. Pp. 408. Philadelphia: F. A. Davis Company, 1936.

Blum's book consists essentially of lists of foods which are advised for consumption and of foods which are to be avoided by persons with various conditions encountered in the practice of medicine. The author presents lists which are captioned so that the physician has merely to find in the index of the book the condition with which he is concerned and then turn to an already prepared list of foods for his patient. The presentation is divided into two parts; the first includes "Dietary for Adults in Health and Disease" and the second "Dietary for Infants and Children in Health and Disease." There are a general index and an index by foods. The diets are based on those the author employed "during a period of twenty years." No references are made to the literature.

Each diet is generalized. The foods are rarely expressed quantitatively and then only in general terms. Brief suggestions and discussions are made in regard to diets and habits of eating. While the diets are generalized in many respects, they are listed for specific types of patients and conditions. For instance, the author has a diet for "chronic indigestion in middle aged adults," for the "spare adult male—impaired digestion," for the "spinster with impaired digestion," for the "frail young mother," for the "professional man" and for the "frail woman school teacher," and there are many other diets specifically captioned. The author uses a different diet for treating obesity in a "woman thirty-five years old" and for treating it in a "two-hundred-and-sixty-pound female clerk." No logical reasons are presented to warrant such minute differentiation. The normal adult is advised to avoid such foods as duck, stew, tongue, goose, kidney, lobster, crab, beets, sprouts, sauces, gravies and many other foods which make up the average normal person's diet. If such commonly consumed foods are to be avoided, the author should at least present reasons. Again, he advises a "professional man" suffering from malnutrition to drink a "glass of water with a teaspoonful of salts, on arising." Why such a practice? The term salts is indefinite in itself.

The book contains a list of foods which leaves the reader wondering why any one of them is selected or eliminated. The diets as listed cannot be intelligently prescribed, nor can they aid the physician in understanding his diet problems. Such a list of foods fosters the use of diets for placebo rather than for therapeutic purposes. The book can be of little use to the medical profession.

La tension mediana dinamica. By Angel Cammarota. Pp. 170. Buenos Aires: El Ateneo; 1936.

In this monograph Cammarota makes a complete study of the "mean arterial tension" in relation to health and disease. The mean arterial tension, as defined by the author, is that constant pressure which at a given time causes the body tissues to have the same energy as the variable tension in the vessels. That pressure, so described, has no relation to the arithmetical mean pressure (one-half the sum of the systolic and diastolic values), and in order to make a distinction it is called the mean arterial tension.

After a preliminary use of several instruments the author chose for his studies the spring oscillograph devised by Frank Soler, of Argentine, and found that the mean arterial pressure varied extensively in different subjects who were apparently in good health; consequently no definite standard figures could be obtained.

Cammarota studied the mean arterial pressure in relation to aortic regurgitation, hypertension and hypotension, arrhythmia, aneurysm, vascular disturbance of the extremities and hyperthyroidism, presenting oscillograms taken at different intervals and complemented when possible with studies made months or even years after the original data were recorded. He arrived at the conclusion that the mean arterial tension has no particular bearing on the diagnosis or prognosis in diseases of the heart and circulatory system.

The author found also that the mean arterial tension may vary considerably within a few minutes and established a definite relationship between it and the systolic and diastolic pressures, especially the latter. Cammarota attributes differences of opinion as well as many errors in experimental contributions to deficiency in the various instruments and devices now in use for studying this particular phase of the blood pressure.

Exophthalmic Goiter and Its Medical Treatment. By Israel Bram, M.D. Foreword by R. G. Hoskins, Ph.D., M.D. Second edition. Price, $6. Pp. 456, with 79 illustrations. St. Louis: C. V. Mosby Company, 1936.

In this edition Bram has employed the same general plan as in the first edition (published in 1920) in presenting his subject. He has, however, increased the scope of each phase of the disease so as to include material that has developed since 1920. Considerably more material is devoted to laboratory tests and case histories. There are fifty-five case histories summarized in the last chapter. The cases were chosen from the author's files and are representative of his "personal experience with over five thousand cases of this disease observed within a period of twenty-five years." The author continues to adhere to medical treatment as the only satisfactory form of therapy for exophthalmic goiter.

The foreword to this edition was written by R. G. Hoskins, Director of Research, the Memorial Foundation for Neuro-Endocrine Research of the Harvard Medical School, who believes that "there is a legitimate place for the partisan . . . in the better sense of the term."

The improvements make the book a good survey of the disease from a clinical standpoint. The author is an extremist on the medical treatment of exophthalmic goiter, but if the reader keeps that in mind when reading the book, he can derive a great deal of benefit from the discussion of the medical treatment of this disease. This is especially true for the radiologists and surgeons, who are inclined to neglect the medical and constitutional aspects of the disease when applying their forms of local therapy.

The Art of Treatment. By William R. Houston, M.D. Price, $5. Pp. 744. New York: The Macmillan Company, 1936.

This is a most interesting and attractive piece of work. The author has attempted to write so as to stimulate intelligent thinking along therapeutic lines, and certainly he has gone far toward accomplishing this aim.

This book is not a textbook on therapeutics in the ordinary sense, little emphasis being laid on drugs and their administration. However, a great deal of independent reasoning and homely philosophy are put forth to drive home the facts that in successful therapy the patient rather than his disease must be treated, that vastly more is *not* known concerning treatment than is known concerning it and, finally, when all is said and done, that most therapeutic conceptions and plans are simple —success turning largely on doing simple things well rather than on carrying out elaborate procedures inadequately.

The book is divided into seven parts, and by all odds the longest part is that which deals with psychotherapy. This long chapter is written sensibly and from an unprejudiced point of view. The entire book is well and clearly written, so

that it makes interesting reading throughout; it is full of valuable hints and suggestions. Surely a book of this type will have a successful career. Not only is it useful for reference purposes, but it affords pleasant reading. It is an admirable contribution toward describing what the art of medical practice amounts to. Medical students, practicing physicians and teachers will all enjoy it.

Endocrinology in Modern Practice. By William Wolf, M.D., Ph.D. Price, $10. Pp. 1018, with 252 illustrations. Philadelphia: W. B. Saunders Company, 1936.

In discussing another book on endocrinology in these columns several years ago the reviewer raised the question of whether any one man could deal adequately with this subject in its present state; it seemed then that the special knowledge of the trained gynecologist, internist, chemist, physiologist and biochemist which had to be synthesized was outside the scope of individual effort. That this point of view is on the whole sound is proved by the character of most of the endocrinologic texts: the books written by those who have worked on the experimental side are usually pitifully defective as to clinical discussion, while those written by clinicians insult the reader with a hash of pseudoscientific physiologic and chemical nonsense. Nevertheless, in the present instance Dr. Wolf has largely surmounted these objections and must be given full and free praise for having produced a really first class all-around book. The style is pleasant and lucid, the reasoning is conservative, the clinical descriptions are excellent and, above all, the summaries of fundamental physiologic knowledge of the endocrine glands are in the best possible accord with recent studies. Here at last is a safe and useful book, free from the "hokum" of the side-show.

Anales del centro de investigaciones tisiologicas. By Prof. Roque A. Izzo. Pp. 175. Buenos Aires: La Semana Médical, 1935.

In the preface of this symposium on tuberculosis the ideals of Dr. Carlos A. Bruchman, senator and physician, are set forth. He conceived the idea of an institution in Buenos Aires the aim of which would be the study of tuberculosis not in general but as found in that community. He felt that such an institution should study the problems of tuberculosis with special reference to the particular social strata, geographic location, habits, foods and racial admixtures found in that particular community. He aptly expressed himself by saying "not tuberculosis in general but our tuberculosis" should be studied.

The fruit of his idea is this initial volume covering the years 1934 and 1935. Under the direction of Prof. Roque A. Izzo this first volume deals with the problems of tuberculosis found in the center. There are a considerable number of case reports, and these do not lack for illustrations of excellent quality. The results obtained with phrenicectomy and thoracoplasty compare well with results reported elsewhere. Other chapters of interest are those dealing with unusual cases of diabetes complicating tuberculosis and albuminuria in pulmonary tuberculosis. There are a considerable number of statistical tables.

The Thyroid. By E. P. Sloan, M.D. Price, $10. Pp. 475, with 99 illustrations. Springfield, Ill.: Charles C. Thomas, Publisher, 1936.

This handsome monograph is somewhat disappointing. Most of it is a compilation, put together in a rather uncritical and disjointed style, of material that is readily available in the current literature. One is given the impression that everything leads up to the chapter on surgery. Here technic and procedure are discussed in detail, and there are some excellent colored plates of the surgical anatomy of the thyroid region. The author properly stresses his own methods, but the final picture of the incision closed by clips, with a drain protruding from the center of the wound, is a shock to those familiar with Halsted's beautiful "silk technic." The reviewer fails to see the point of the reproduction on the title page of the bronze cast of Dr. Sloan's hands.